

RAPID COMMUNICATION

Validation of simple indexes for nonalcoholic fatty liver disease in western China: a retrospective cross-sectional study

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Abstract. Various noninvasive algorithms have been developed for predicting the presence of nonalcoholic fatty liver disease (NAFLD). The evaluation of the indexes' diagnostic performance has been reported in Europe and Asia over the past decade; however, external validation of them in China is rare. This study was aimed to evaluate various indexes for NAFLD in western China. It was a retrospective cross-sectional study, using data from a large-scale health check-up project at Sichuan provincial hospital. Receiver operating characteristic (ROC) curves of eight indexes, including the fatty liver index (FLI), the hepatic steatosis index, lipid accumulation product and *etc.*, were developed to predict ultrasonographic NAFLD. There were 13,122 subjects in this study (2,692 NAFLD patients and 10,430 non-NAFLD participants). The area under ROC curve of FLI for predicting NAFLD was 0.880 (95% confidence interval, 0.874–0.886), which was significantly higher than other seven indexes. Accuracy, sensitivity and specificity of FLI for NAFLD were good (cut-off value = 30, 0.782, 0.832, 0.770 and cut-off value = 60, 0.838, 0.443, 0.940, respectively). Furthermore, FLI also presented advantages in expenditure and accessibility, compared with other indexes. It supports FLI as an easily accessible index for physicians and a reliable predictor for NAFLD screening in western China.

Key words: Nonalcoholic fatty liver disease, Non-invasive diagnosis, Fatty liver index, Hepatic steatosis index, Lipid accumulation product

RECENT ADVANCE suggests nonalcoholic fatty liver disease (NAFLD) as the liver disease component of metabolic syndrome [1]. The global prevalence of NAFLD

has rapidly increased in parallel with the rising population of obesity and diabetes [2]. Its prevalence in the US is reported to be between 10% and 30%, with similar rates found in Europe and Asia [3].

The astonishing number of NAFLD patients with potential for progressive liver diseases generates challenges for population screening. Furthermore, the higher liver-related morbidity/mortality and the increased risks of type 2 diabetes and cardiovascular diseases had been indicated in NAFLD patients [4].

Various noninvasive algorithms, based on metabolic and anthropometric variables, have been developed for predicting NAFLD [5]. The fatty liver index (FLI) [5], the hepatic steatosis index (HSI) [6] and lipid accumulation product (LAP) [7] have been derived and utilized to screen hepatic steatosis in large epidemiologic studies or identify potential patients for further examination in clinical practice. The evaluation of the indexes' diagnostic

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Abbreviations: ALT, Alanine transaminase; AST, Aspartate transaminase; AUROC, Area under receiver operating characteristic; BMI, body mass index; FLD index, Fatty liver disease index; FLI, Fatty liver index; FPG, Fasting plasma glucose; FSI, Framingham Steatosis Index; GGT, γ -Glutamyltransferase; HDL-C, High-density lipoprotein cholesterol; HSI, Hepatic steatosis index; LAP, Lipid accumulation product; LDL-C, Low-density lipoprotein cholesterol; NAFLD, Nonalcoholic fatty liver disease; TC, Total cholesterol; TG, Triglycerides; WHR, waist-to-hip circumference ratio

performance has been reported in Europe [8] and Asia [9, 10] over the past decade; however, external validation of them in western China is rare.

This study is aimed to evaluate eight indexes for predicting NAFLD in a large population in western China, using ultrasound as the reference standard.

Methods

Subjects

It was a retrospective cross-sectional study. There were 24,134 consecutive examinees receiving health check-up services at Sichuan Provincial People's Hospital from January to March 2016. All subjects gave written informed consent before participation. This study was approved by the Ethics Committee of Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, in accordance with the Helsinki Declaration in 1975.

Exclusion criteria

We excluded subjects who had: 1) uncompleted clinical data; 2) significant alcoholic consumption (men >140 g or women >70 g per week in the past 12 months) [11]; 3) viral/autoimmune hepatitis, drug-induced liver damage or other liver diseases.

Clinical examines

Anthropometric and biochemical examinations, as well as upper abdominal ultrasonography, were performed as described before [12]. All subjects were informed to complete an overnight fast. About 10 mL whole blood samples were collected from each subject, and then serum samples were separated for immediate analysis. Serum analyses were measured using a Hitachi 7600 Auto-Analyzer (Hitachi, Tokyo, Japan) or an Abbott-Architect Immunoanalyzer (Abbott Laboratories, Lake Bluff, Illinois, USA). Real-time ultrasonography of the upper abdominal organs was performed for each subject by ten experienced doctors using General Electric LOGIQ E9 (General Electric, Fairfield, Connecticut, USA). The ultrasonographic doctors were unaware of the anthropometric and biochemical results.

Definition of NAFLD

NAFLD was diagnosed according to the Guidelines for Diagnosis and Treatment of NAFLD issued by Fatty Liver and Alcoholic Liver Disease Study Group of the Chinese Liver Disease Association [11]. The working

definition of NAFLD includes: 1) liver imaging meet the diagnostic criteria and cannot be explained by other reasons (e.g. alcohol drinking <140 g/w in men or <70 g/w in women); or 2) subjects with metabolic syndrome presented elevated serum liver enzymes (>6 months).

Predicting indexes for NAFLD

The eight indexes in this study were listed in Table 1.

Expenditure of indexes

The expenditure of each indexes were calculated, based on the website of Beijing Medical Service [13].

Statistical methods

Baseline analyses were performed by using descriptive statistics. The Student's *t* test or Mann-Whitney U test for continuous variables, and χ^2 test or Kruskal-Wallis test for categorical variables were used to compare the parameters between two groups. Receiver operating characteristic (ROC) curves of various indexes were developed to predict the presence of NAFLD. Comparisons between areas under receiver operating characteristic (AUROC) curves of FLI and other indexes were performed, using the method of DeLong *et al.* [14]. All statistical analyses and plotting were performed using Stata (version MP 11.2, StataCorp LP, College Station, TX, USA) and SPSS (version 21.0, SPSS Inc., Chicago, IL, USA). A two-sided $p < 0.05$ was considered statistically significant.

Results

As shown in Fig. 1, there were a total of 24,134 subjects initially in the project. After exclusion due to declined invitation, uncompleted data, and other medical reasons, there were 13,122 subjects participated in this study, including 2,692 NAFLD patients and 10,430 non-NAFLD participants. The general characteristics by NAFLD are indicated in Table 2. Based on the annual examine in Sichuan province, the prevalence of NAFLD was 20.52%. The NAFLD patients were older (49.14 ± 13.17 years vs. 45.98 ± 14.86 years, $p < 0.001$) and presented a higher proportion of male (77.9% vs. 48.5%, $p < 0.001$), compared with the non-NAFLD subjects.

In Table 3, AUROC of FLI for predicting NAFLD was 0.880 (95% Confidence interval [CI], 0.874–0.886). It was significantly higher than AUROC of Fatty liver disease index (FLD index) (0.874; 95% CI, 0.867–0.881; $p = 0.006$), Framingham Steatosis Index (FSI) (0.864; 95%

Table 1 The indexes for predicting hepatic steatosis in this study

Authors, year, reference	Country	Index's name	Number of subjects	Number of variables	Formula
Bedogni, G. <i>et al.</i> 2006 [6]	Italy	Fatty liver index (FLI)	496	4	$FLI = \frac{(e^{0.953 \cdot \log TG + 0.139 \cdot BMI} + 0.718 \cdot \log GGT + 0.053 \cdot WC - 15.745)}{(1 + e^{0.953 \cdot \log TG + 0.139 \cdot BMI + 0.718 \cdot \log GGT + 0.053 \cdot WC - 15.745})} * 100$
Bedogni, G. <i>et al.</i> 2010 [8]	Italy	Lipid accumulation product (LAP)	588	3	LAP (men) = (WC - 65) * TG LAP (women) = (WC - 58) * TG
Lee, J. H. <i>et al.</i> 2010 [7]	South Korea	Hepatic steatosis index (HSI)	Derivation 5,360 Validation 5,364	5	HSI = 8*(ALT/AST ratio) + BMI (+2, if female; +2, if diabetes)
Park, Y. J. <i>et al.</i> 2011 [31]	South Korea	Korea index*	456	5	Korea index* is calculated based on the following: ALT/AST ratio >1.5, GGT >50 U/L, TG >150 mg/dL (above items +1 score, individually), BMI 23–24.9 (+2 scores) or BMI >25 (+3 scores)
Fuyan, S. <i>et al.</i> 2013 [26]	China	Fatty liver disease index (FLD index)	Derivation 3,464 Validation 3,462	5	FLD index = BMI + TG + 3*(ALT/AST ratio) + 2*Hyperglycemia (yes = 1, no = 0)
Ichino, N. <i>et al.</i> 2015 [24]	Japan	NAFLD index	Derivation 673 Validation 272	6	NAFLD index (men) = -15.5693 + 0.3264*BMI + 0.0134*TG NAFLD index (women) = -31.4686 + 0.3683*BMI + 2.5699*albumin + 4.6740*(ALT/AST ratio) - 0.0379*HDL-C
Wang, J. <i>et al.</i> 2015 [25]	China	ZJU index	Derivation 4,800 Validation 4,802	6	ZJU index = BMI + FPG + TG + 3*ALT/AST ratio (+2, if women)
Long, M. T. <i>et al.</i> 2016 [30]	USA	Framingham steatosis index (FSI)	Derivation 1,181 Validation 4,489	8	FSI = -7.981 + 0.011*age - 0.146*sex (female = 1, male = 0) + 0.173*BMI + 0.007*TG + 0.593*hypertension (yes = 1, no = 0) + 0.789*diabetes (yes = 1, no = 0) + 1.1*ALT/AST ratio ≥ 1.33 (yes = 1, no = 0).

Indexes were ordered by released year. Derivation, Derivation cohort; Validation, Validation cohort. *No official name. ALT, Alanine transaminase; AST, Aspartate transaminase; FPG, Fasting plasma glucose; GGT, γ -Glutamyltransferase; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TC, Total cholesterol; TG, Triglycerides; WC, Waist circumference.

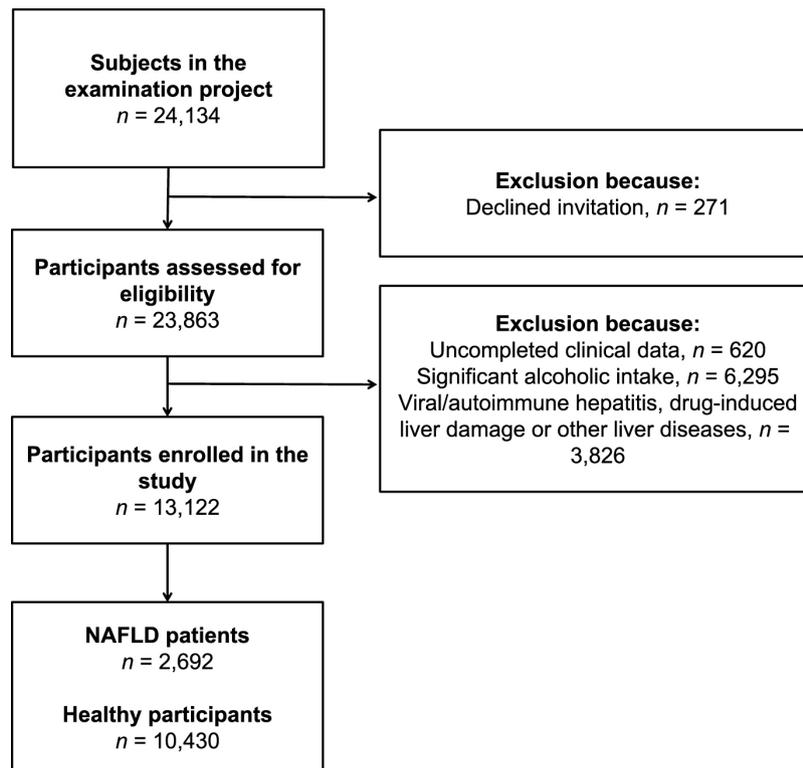


Fig. 1 Flow chart of participants' inclusion

Table 2 Characteristics of subjects according to NAFLD

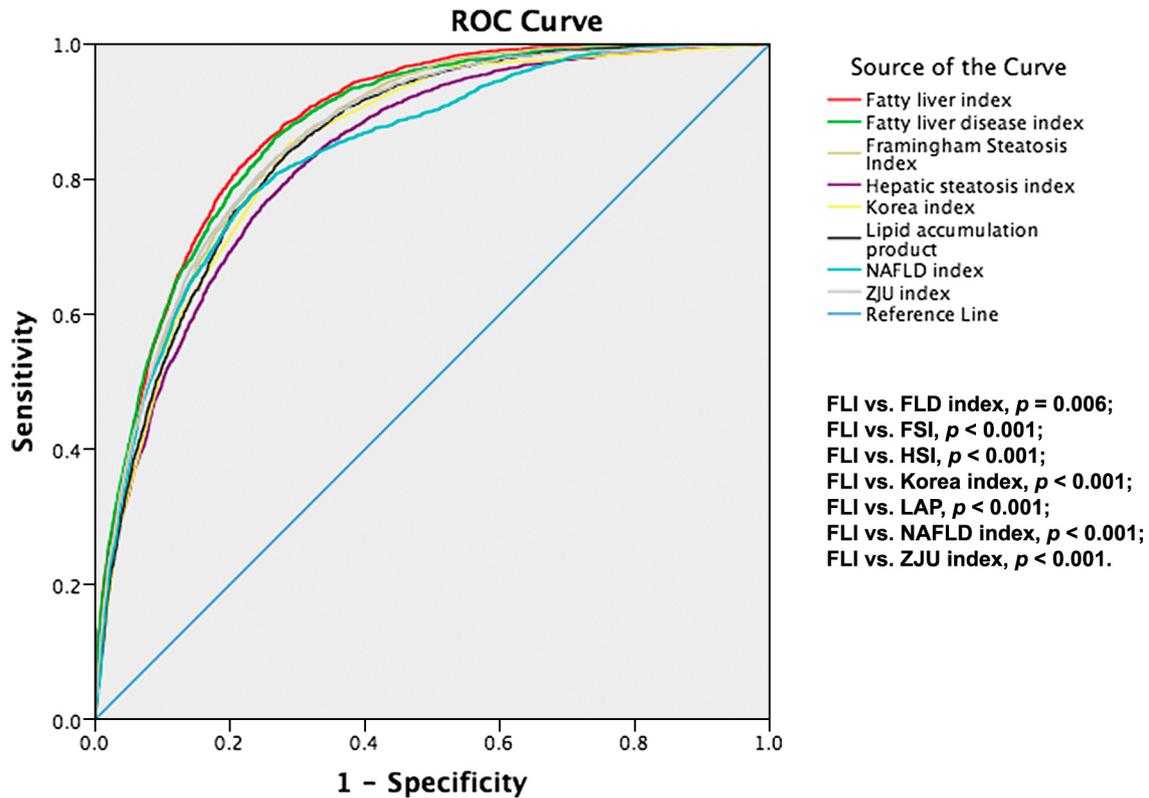
Parameter	Control	NAFLD	<i>p</i> value
No. of subjects	10,430	2,692	
Age (years)	45.98 ± 14.86	49.14 ± 13.17	<0.001
Male, <i>n</i> , %	5,058, 48.5%	2,096, 77.9%	<0.001
BMI (kg/m ²)	22.63 ± 2.84	26.46 ± 2.86	<0.001
WHR	0.84 ± 0.07	0.91 ± 0.05	<0.001
ALT (U/L)	19.00 (14.00–27.00)	33.00 (23.00–48.00)	<0.001
AST (U/L)	24.00 (20.00–29.00)	29.00 (24.00–36.00)	<0.001
ALT/AST ratio	0.80 (0.62–1.05)	1.16 (0.88–1.49)	<0.001
GGT (U/L)	18.00 (13.00–28.00)	36.00 (24.00–58.00)	<0.001
TG (mmol/L)	1.11 (0.81–1.59)	2.02 (1.43–2.93)	<0.001
TC (mmol/L)	4.77 (4.19–5.39)	5.04 (4.43–5.72)	<0.001
HDL-C (mmol/L)	1.37 (1.16–1.61)	1.11 (0.97–1.30)	<0.001
LDL-C (mmol/L)	2.92 (2.35–3.45)	3.13 (2.56–3.73)	<0.001
FPG (mmol/L)	4.94 (4.56–5.35)	5.26 (4.76–5.94)	<0.001

Data are mean ± standard deviation or median (interquartile range) for continuous variables; *p* values present comparisons between NAFLD patients and non-NAFLD subjects. Abbreviations: ALT, Alanine transaminase; AST, Aspartate transaminase; BMI, body mass index; FPG, Fasting plasma glucose; GGT, γ -Glutamyltransferase; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TC, Total cholesterol; TG, Triglycerides; WHR, waist-to-hip circumference ratio.

Table 3 Areas under receiver operating characteristics curves of various indexes for predicting NAFLD

Predicting index	Area under the curve	Standard Error	<i>p</i> value	95% Confidence Interval	
				Lower Bound	Upper Bound
Fatty liver index	0.880	0.003	<0.001	0.874	0.886
Fatty liver disease index	0.874	0.003	<0.001	0.867	0.881
Framingham Steatosis Index	0.864	0.003	<0.001	0.857	0.871
Hepatic steatosis index	0.833	0.004	<0.001	0.825	0.841
Korea index	0.847	0.004	<0.001	0.840	0.855
Lipid accumulation product	0.853	0.004	<0.001	0.845	0.860
NAFLD index	0.839	0.004	<0.001	0.831	0.847
ZJU index	0.861	0.004	<0.001	0.854	0.868

Indexes were ordered alphabetically.

**Fig. 2** Receiver operating characteristic curves of the indexes

Comparisons between areas under receiver operating characteristic (AUROC) curves of FLI and other indexes were performed, using the method of DeLong *et al.* Indexes were ordered alphabetically. Abbreviations: FLI, Fatty liver index; FLD index, Fatty liver disease index; FSI, Framingham Steatosis Index; HSI, Hepatic steatosis index; LAP, Lipid accumulation product.

CI, 0.857–0.871), HSI (0.833; 95% CI, 0.825–0.841), Korea index (0.847; 95% CI, 0.840–0.855), LAP (0.853; 95% CI, 0.845–0.860), NAFLD index (0.839; 95% CI,

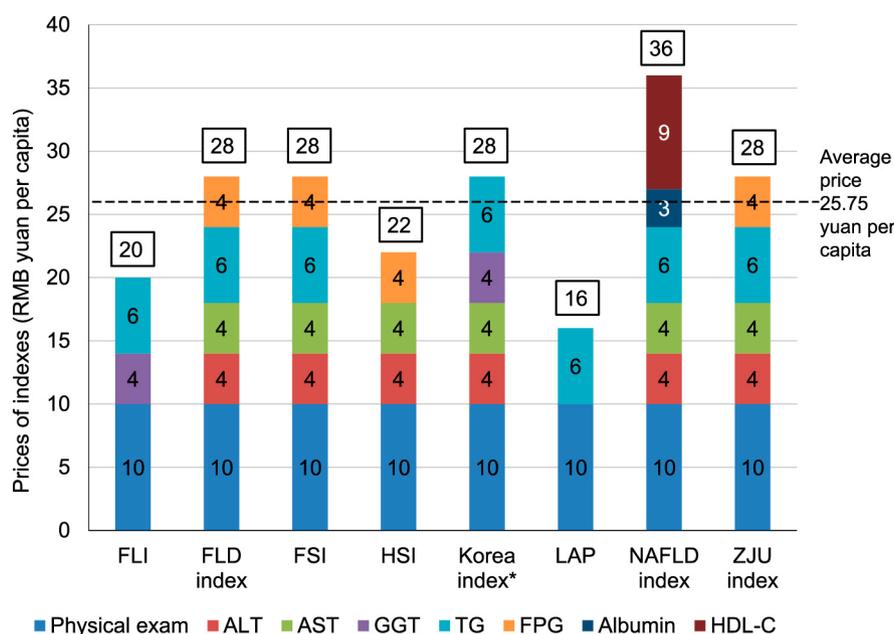
0.831–0.847), or ZJU index (0.861; 95% CI, 0.854–0.868; the latter six *p* values all <0.001; Fig. 2).

According to the cut-off values proposed by Bedogni

Table 4 Diagnostic performance of Fatty liver index

Index	Cut-off value	Accuracy	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Fatty liver index	30.0	0.782	0.832	0.770	0.482	0.947	3.612	0.218
	30.4195	0.785	0.829	0.774	0.487	0.946	3.672	0.221
	60.0	0.838	0.443	0.940	0.657	0.867	7.425	0.593

Abbreviations: NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio; PPV, positive predictive value.

**Fig. 3** Expenditure of indexes

Indexes were ordered alphabetically. *Korea index, no official name. The prices of each index were calculated based on the Medical Service of Beijing. Age, sex, weight, height, waist circumference and medical history were obtained by physical exam. Numbers on the top of the columns indicate the total prices of the indexes, per capita. Abbreviations: FLI, Fatty liver index; FLD index, Fatty liver disease index; FSI, Framingham Steatosis Index; HSI, Hepatic steatosis index; LAP, Lipid accumulation product.

et al. [5], accuracy, sensitivity and specificity of FLI <30 for predicting absence of NAFLD were 0.782, 0.832 and 0.770, respectively. When the cut-off value came to ≥ 60 for predicting presence of NAFLD, accuracy, sensitivity and specificity were 0.838, 0.443 and 0.940, respectively. The best cut-off value was 30.4195 (accuracy 0.785, sensitivity 0.829, and specificity 0.774) (Table 4).

Based on the price of Beijing Medical Service, the average expenditure of eight indexes was 25.75 Yuan (Chinese currency) per capita (Fig. 3). The lowest price was LAP that only cost 16 Yuan per capita, followed by FLI (20 Yuan per capita). The highest price was NAFLD index that cost 36 Yuan per capita.

Discussion

In this study, we provided external validation of eight indexes, based on simple clinical parameters, for predicting NAFLD in a 13,122 participants of a large-scale cross-sectional study in western China. It indicates that FLI has good predictive values for ultrasonographically diagnostic NAFLD with a good AUROC of 0.880. It supports FLI as an adequate marker of NAFLD for population screening in western China.

NAFLD has become an emerging public health concern, given its remarkable growth in the worldwide over the recent decades [15]. Specifically, due to the westerni-

zation of lifestyle and the aging population, the prevalence of NAFLD, closely related with metabolic disorders such as central obesity, hypertriglyceridemia and insulin resistance, has witnessed a rapid increase in Asia [16, 17].

Most NAFLD patients do not present specific symptoms, particularly at the early stage, which hinders prevention and early detection [18]. Even though liver biopsy is regarded as the gold standard for liver steatosis, it is not routinely performed due to its invasive procedure and frequent sampling error [1, 19]. Moreover, other radiological techniques, *e.g.* magnetic resonance imaging and spectroscopy, are limited in clinics because of expense and unfeasibility for population screening [19]. Thus, the diagnosis of NAFLD in population-based studies is usually made by ultrasound [20].

Recently, Jamali R *et al.* [21, 22] performed a case-control study to establish models based on serum adipokines for discriminating healthy, simple steatosis and NASH. NAFLD discriminant score, includes serum levels of adiponectin, visfatin, IL-6, and TNF- α , correctly classified 86.4% NAFLD cases from the controls (91% sensitivity and 83% specificity). Besides, NASH discriminant score, includes adiponectin, visfatin, IL-8 and TNF- α , differentiated 84% NASH cases from cases of simple steatosis (90% sensitivity and 66% specificity). The study introduced two models for discriminating NAFLD/NASH from healthy controls/simple steatosis based on a panel of serum markers. The models demonstrated great accuracy and showed decent sensitivity and specificity. It will be meaningful to validate the models in East Asia in the future.

Ten years ago, Bedogni *et al.* [5] firstly established a formula to calculate FLI, based on four feasible parameters, to predict ultrasonographic fatty liver in the Dionysos Nutrition & Liver Study. The following studies found that this simple and non-invasive algorithm presented excellent discriminative ability to determine NAFLD. After that, Bedogni *et al.* [7] also proposed LAP as a very simple test to indicate the presence of hepatic steatosis. In Asia, Lee *et al.* [6] developed HSI, using a cross-sectional study in Seoul, South Korea, while Ichino *et al.* [23] derived a screening tool, named the NAFLD index, in Hokkaido, Japan. Besides, Wang *et al.* [24] and Fuyan *et al.* [25] proposed ZJU index and FLD index, individually, in eastern China. The early identification of NAFLD might help: 1) improve the early select the high-risk population of hepatic steatohepatitis and fibrosis; 2) given the natural history, improve

the clinical management of metabolic syndrome, diabetes and cardiovascular disease; 3) the application of non-invasive indexes may help the selection of potential population before imaging tests, which lowers the cost.

A series of predicting indexes was developed and validated individually in Europe and Asia [10, 26, 27]. Few studies were conducted to appraise indexes in western China, which witnesses a variety of differences in culture, diet and lifestyle in comparison to eastern China. In this study, eight indexes, *i.e.* FLI [5], LAP [7, 28] (derived in Europe), FSI [29] (derived in USA), FLD index [25], HSI [6], Korea index (by Park *et al.* [30], no official name), NAFLD index [23] and ZJU index [24, 31] (derived in East Asia), were included and validated, using a large population of 13,122 subjects in western China. This study confirmed the significance of FLI as a predictor of NAFLD. FLI presented a better discriminative ability for detecting ultrasonically diagnostic NAFLD than other seven reported indexes. Furthermore, in the formula of FLI, there are four variables that are less than most of others, except LAP. Lastly, it only costs 20 Yuan per capita to obtain the results of all parameters, which is lower than the average price of 25.75 Yuan. Even though FLI presented various advantages, it still had some limitations. By comparing the subjects' characteristics of FLI successful and failed prediction (Supplementary Table 1), the successful group was younger than the failed group, while the sexual ratios between two groups were different. Besides, FLI tended to be an index better ruling out the non-NAFLD subjects rather than identifying the NAFLD, who had higher liver enzymes and lipid/glucose profile.

Recently, Li *et al.* [32] published a study that validated five indices for identifying NAFLD in a Chinese population, which indicated a higher AUROC value by the ZJU index than the values for the other models includes FLI. There were three differences between two studies. Firstly, the prevalence of NAFLD in our study was 20.5% that was close to the average level based on a number of population-based surveys [15], while the study of Li *et al.* reported a prevalence of 37.0%. We believe our study could present a current situation of NAFLD in western China. Secondly, the characteristics of the population, *e.g.* the age distribution and the sex proportion, were different, which might partly explain the inconsistency between the two studies. Lastly, our study validated eight simple indices for NAFLD, and evaluated the expenditure of each index.

The strength of this study, to our knowledge, is one of

the largest validation studies that reported eight non-invasive indexes for predicting NAFLD in Asians. However, it has some limitations. To begin with, the participants that afforded the expense of the annual physical checkup in the urban area tend to have higher socioeconomic status, which might lead to a higher prevalence of NAFLD [15] and a selection bias. Meanwhile, the expenditure of the indexes was evaluated based on the price of Beijing Medical Service. Thus, the results cannot simply be extrapolated to the general population. Secondly, we used ultrasonography as a diagnostic tool for hepatic steatosis [1, 20, 33], therefore it might result in: 1) the underestimated prevalence of NAFLD; 2) the inter- and intra-variations of diagnosis among ten ultrasonic doctors were unavailable; 3) severity of liver steatosis failed to be included and analyzed in this study. The third limitation was the ability to adjust for other potential confounders, such as diet and family history, which are related with metabolic risk and liver diseases. Lastly, this study was the retrospective design, thus further prospective studies are required.

Several indexes have been developed based on clinical and laboratory parameters for screening of NAFLD in serial studies of large population. Assessment of variables in the indexes is accessible and safe. However, given the large population in this health check-up projec-

tion, ultrasound was chosen to be the diagnostic methods of NAFLD. We need further histological study to validate and compare the cost-effectiveness and accuracy between indexes and ultrasound, using biopsy as the golden standard.

In conclusion, we validated various simple indexes for predicting NAFLD in a large-scale cross-sectional study. Owing to the high incidence of NAFLD in the community population and uncertainties about ultrasonographic screening, a noninvasive index may help medical practitioners select subjects for ultrasonographic screening. It supports FLI as an easily accessible index and a reliable predictor for NAFLD screening in western China.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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