Utility of different indices in screening Chinese postmenopausal women for hepatic steatosis

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ABSTRACT

Background and Objectives: To analyze the potential of fatty liver index (FLI) and several obesity indices and to explore which index is best for predicting nonalcoholic fatty liver disease (NAFLD) in Chinese postmenopausal women. **Methods and Study Design:** A cross-sectional study was conducted in 680 Chinese postmenopausal women. NAFLD was defined as a hepatic steatosis observed on liver ultrasonography in the absence of a second cause. Odds ratio and corresponding 95% confidence interval (CI) between hepatic steatosis and FLI as well as different obesity indices were evaluated by Binary Logistic regression model. Receiver operating characteristic curve and area under curve (AUC) were used to compare the ability of predicting hepatic steatosis between FLI and obesity indices. **Results:** The upper values of all indices were significantly associated with the presence of hepatic steatosis (all $p<0.01$) after the adjustment for potential confounders. The largest AUC [0.85 (0.82-0.88), 95% CI, $p<0.01$] was observed for FLI, followed by the frequently used obesity indices. **Conclusions:** FLI is closely associated with the presence of hepatic steatosis in Chinese postmenopausal women. Compared to the obesity indices frequently used, FLI is a better surrogate marker for predicting the presence of hepatic steatosis in Chinese postmenopausal women.

Key Words: non-alcoholic fatty liver disease, hepatic steatosis, fatty liver index, visceral adiposity index, obesity

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by excessive triglyceride accumulation in hepatocytes without the presence of excessive alcoholic consumption or other definite injures to the liver, and it represents a spectrum of hepatic injures ranging from simple nonalcoholic fatty liver disease (steatosis) to nonalcoholic steatohepatitis and hepatic cirrhosis.[1,2] As the most common form of chronic liver disease, NAFLD affects 24% to 42% of people in Western countries and 5% to 40% in Asian countries.[3-5] In China, NAFLD has become one of the major causes of chronic liver disease, and its prevalence in Chinese adults has reached 20.1%.[6] NAFLD is not only the hepatic components of metabolic syndrome, but also a risk factor for various metabolic disorders including type 2 diabetes, insulin resistance, dyslipidemia, and cardiovascular events.[7,8] Therefore, it has been recognized as an emerging health problem worldwide.

NAFLD is closely associated with obesity, and the prevalence of NAFLD was significantly increased along with the increased ranges of obesity indices. In women, it seems that menopausal status is associated with hepatic steatosis.[9,10] Compared to men, the prevalence of NAFLD in women was lower before menopause but was higher after menopause,[11] which might be explained by a decline in estrogen level that leads to hepatic steatosis through a reduction of fatty acid oxidation and an increase in lipogenesis within the liver.[12] In addition, postmenopausal women accumulate more fat in the intra-abdominal region than do premenopausal women and subsequently have a greater risk of developing metabolic disorders, which is closely linked with NAFLD.[13] Consequently, it is important to explore a simple and effective method to screen NAFLD in postmenopausal women.

A liver biopsy is the gold standard for NAFLD diagnosis, but this method has limited diagnostic value in a population-based study due to its invasive nature.[14] In clinical settings, an abdominal ultrasonography is the most common technique used to assess the presence of NAFLD. However, abdominal ultrasonography is also expensive and laborious for study participants.[15] Thus, several studies have evaluated the potential of some simple indices for screening NAFLD.[16-18] A study showed that waist circumference (WC) and waist-to-height ratio (WHtR) were as useful as dual-energy X-ray absorptiometry (DXA) and computed tomography (CT) for predicting NAFLD in adults aged 20-88 years.[16] Another study reported that WHR was an effective anthropometric indicator to screen NAFLD.[17] Bedogni et al developed a simple scoring system called the fatty liver index (FLI) as a predictor of fatty liver disease,[18] and several studies have reported that NAFLD assessed by FLI was well-correlated with hepatic steatosis using abdominal ultrasonography in a general population.[19,20] However, the validation of FLI is still to be evaluated in Chinese populations. Recently, the AlkaMeSy Study Group has reported an index called visceral adiposity index (VAI) to evaluate body fatness, and this index has been used as a marker of both visceral fat dysfunction and an individual's subsequent cardio-metabolic risk.[21] Recently there have been several studies regarding evaluating the association of VAI with NAFLD and their results are controversial.[22-25] However, to the best of our knowledge, there are still no studies regarding comparing FLI with those obesity indices, including body mass index (BMI), WC, WHtR, waist-to-hip ratio (WHR), and VAI in screening hepatic steatosis among Chinese postmenopausal women. Therefore, the objectives of this study are to analyze the potential of FLI and different obesity indices and to explore which index is best for predicting NAFLD in Chinese postmenopausal women, which may help physicians select subjects for liver ultrasonography, and researchers to select patients for epidemiologic studies.

MATERIALS AND METHODS

From July to September 2016, there were 787 postmenopausal women who voluntarily visited the Medical Examination Center of Peking Union Medical College Hospital, China Academic Medical Science and Peking Union Medical College (Beijing, China), for a health checkup. All women were invited to participate in this study, and 39 women disagreed with participation. Thereafter, a standard questionnaire was used by trained physicians to collect relevant information of the rest of the participants (n=748), including age, date of the final menstruation, smoking status (smoker, exsmoker or nonsmoker), drinking status (drinker, exdrinker or nondrinker) as well as alcohol intake, medical history and medication use, and then blood pressure recordings were obtained from the right arm of all the participants in a sitting position and the related measurements were performed (women who volunteered to participate in this study should provide written informed consent before participation). Hepatic steatosis was observed on liver ultrasonography. Of the 748 women, participants were excluded if they had any of the following criteria: 1) alanine aminotransferase (ALT) >70 U/L and/or aspartate aminotransferase (AST) >70 U/L and/or γ-glutamyltransferase (γ-GGT) >70 U/L (In order to rule out the individuals with suspected other liver disease); 2) a significant history of alcohol intake >10 g of ethanol per day; 3) a history of chronic viral liver disease and/or autoimmune liver disease, liver insufficiency, inflammatory bowel disease, and malignancy; 4) a history of the use of steatogenic medications (corticosteroids, etc); and 5) did not participate in the weight loss program. At last, a total of 680 postmenopausal women were enrolled in this study. All women were naturally postmenopausal women (aged 42-59 years) who had amenorrhea for at least 12 months after their final menstruation and did not have any pathological cause of amenorrhea.[26,27]

This study was approved by the Ethics Committee of Peking Union Medical College Hospital, China Academic Medical Science. All participants provided written informed consent before participating in this study.

Anthropometric measurements

Anthropometric measurements of individuals wearing light clothing and without shoes were conducted by well-trained examiners. Height was measured to the nearest 0.1 cm with a portable stadiometer. Weight was measured in an upright position to the nearest 0.1 kg with a calibrated scale. BMI was calculated by dividing weight (kg) by height squared (m^2). WC measurements were taken at the end of normal expiration to the nearest 0.1 cm, measuring from the midway between the lower borders of the rib cage and the iliac crest. Hip

circumference was obtained at the widest point between the hip and the buttocks. WHR and WHtR were then calculated.

Biochemical measurements

Blood sample were collected from the subjects' peripheral vein in the morning after a fasting period of 10-12 h. the samples were immediately centrifuged at 4°C, and plasma was assayed for lipid profile including total cholesterol (TC),triglyceride (TG), and high-density-lipoprotein cholesterol (HDL-c) and low-density-lipoprotein cholesterol (LDL-c); and fasting blood glucose(FBG), high sensitivity C-reactive protein(CRP), ALT, AST, and γ-GGT, using an automated analyzer (Olympus AU5800, Japan).

Evaluation criteria

In the present study analysis, the obesity indices included BMI, WC, WHtR, WHR, and VAI. According to Cooperative Meta-analysis Group of China Obesity Task Force, BMI were divided into three groups, normal (<24.0 kg/m^2), overweight (24.0-27.9 kg/m^2), and obesity (≥28.0 kg/m^2).[28] The cut-off point of WC was 80 cm for women.[27] A WHtR of ≥0.50 or a WHR of ≥0.85 was defined as a central obesity. [29-31]

VAI, a sex-specific index based on WC (cm), BMI (kg/m^2), TG (mmol/L), and HDL-c (mmol/L) and indirectly expressing visceral fat function, was calculated as follows: [21]

Females: VAI= [WC/ (39.58 + 1.89 × BMI)] × (TG / 0.81) × (1.52 / HDL)

To date, there is no suitable cut-off value of VAI to define obesity. Therefore, VAI was grouped by quartiles, and the cut-off points of VAI quartiles were 1.1, 1.6, and 2.5 among all the women.

The FLI was calculated according to a previously published report by Bedogni et al.:18

$[e^{0.953 \times \log e (TG) + 0.139 \times BMI + 0.718 \times \log e (GGT) + 0.053 \times \text{waist circumference} - 15.745)}] / [1 + e^{0.953 \times \log e (TG) + 0.139 \times BMI + 0.718 \times \log e (GGT) + 0.053 \times \text{waist circumference} - 15.745}] \times 100$, with triglycerides measured in mg/dL, GGT in U/L, and WC in cm. FLI were divided into three groups, low (<30), intermediate (30-59), and high (≥60).

Ultrasonography for liver and criteria of NAFLD

NAFLD was defined as the presence of definite hepatic steatosis on ultrosonography, such as a bright hepatic echo pattern, increased attenuation of the echo beam and loss of intrahepatic architectural detail without a secondary cause.[32,33] Ultrosonography of the liver was performed using a 3.5-MHz conves-array probe and a 7.5-MHz linear-array probe (Nemio 30,

Toshiba, Japan) by an experienced examiner who was unaware of the laboratory and other results.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS version 11.5, Chicago, IL, USA). The independent-sample t-test was used to compare continuous variables between NAFLD group and the control group. Categorical variables were represented by frequency or percentage and examined by X^2 test. A Binary logistic regression analysis was performed to estimate the associations of hepatic steatosis with FLI and obesity indices with the adjustment for age, lifestyle variables, blood pressure, history of hypertension and diabetes, fasting blood glucose, TC, LDL-c and hs-CRP. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was applied to compare the predictive potential for hepatic steatosis among FLI, BMI, WC, WHtR, WHR, and VAI. All reported *p* values were two-tailed, and $p<0.05$ was considered statistically.

RESULTS

The basic characteristics of NAFLD group and control group

The characteristics of the study participants are presented in Table 1. Of the 680 postmenopausal women, 227 were detected in the presence of fatty liver. Compared with the control group, the NAFLD group had significantly higher BMI, WC, WHtR, WHR, VAI, FLI, systolic blood pressure, diastolic blood pressure, GGT, ALT, FBG, TG, LDL-c, and hs-CRP, but lower HDL-c. In addition, the prevalence of type 2 diabetes, and hypertension were significantly higher in NAFLD group than those in control group. No significant differences in the level of AST were found between the two groups.

Odds ratio and 95% confidence interval (CI) for the presence of hepatic steatosis according to the corresponding cutoff values for fatty liver index as well as obesity indices

According to Binary logistic regression analysis, the upper values of FLI as well as all obesity indices had the significantly higher odds ratio (OR) for hepatic steatosis (all $p<0.001$) than their respective reference after adjusting for age, lifestyle variables, blood pressure, TC, LDL-c, ALT, AST, blood glucose levels, history of diabetes and hypertension, and hs-CRP levels (Table 2).

ROC curve analysis of NAFLD-associated indicators of hepatic steatosis

FLI and obesity indices, including BMI, WC, WHtR, WHR, and VAI, showed significant areas under the ROC curve. Among of them, the largest AUC was observed for FLI [0.85(0.82-0.88), 95% CI, p<0.01], followed by WHR [0.77(0.74-0.81), 95% CI, p<0.01], WC [0.77(0.74-0.81), 95% CI, p<0.01], VAI [0.77(0.73-0.81), 95% CI, p<0.01], BMI [0.77(0.73-0.80), 95% CI, p<0.01], and WHtR [0.77 (0.73-0.80), 95% CI, p<0.01] (Table 3 and Figure 1). In summary, a conceptual diagram representing the predictive ability of commonly used screening indices for hepatic steatosis in postmenopausal women is provided (Figure 2).

DISCUSSION

To the best of our knowledge, this study is the first cross-sectional study to examine and compare the discriminatory potentials of FLI and several obesity indices for predicting NAFLD in Chinese postmenopausal women. The present study showed that the upper values of FLI as well as all obesity indices had the significantly higher odds ratio for hepatic steatosis than their respective reference after adjusting for the confounders, implying that both FLI and obesity indices including BMI, WC, WHtR, WHR, and VAI could be used as the markers to predict the presence of NAFLD. Although FLI was positively associated with all the obesity indices (including BMI, WC, WHtR, WHR, and VAI) and all indices showed significant areas under the ROC curve, the largest AUC was observed for FLI among all the indices. It seems that FLI is a better surrogate marker for predicting the presence of hepatic steatosis in Chinese postmenopausal women compared to the obesity indices frequently used.

NAFLD is highly prevalent in Western countries and Asian countries. It is often linked to obesity and the presence of metabolic syndrome. With the introduction of westernized lifestyle and increasing frequency of obesity in the Asia-Pacific region, the prevalence of NAFLD has increased rapidly over the past two decades.[34-37] Cross-sectional and longitudinal Asian studies confirmed the close link between fatty liver and underlying insulin resistance as well as metabolic syndrome,[38] and the latter was present in approximately 70% of Chinese subjects with NAFLD.[39] The clinical importance of NAFLD stems not only from its increasing prevalence in the general population but also its potential to progress to cirrhosis and liver failure.[40] In addition, NAFLD is closely associated with type 2 diabetes risk, cardiovascular damage and cardiovascular events.[6,7,41]

FLI is an index firstly reported by Bedogni et al and its score ranges from 0 to 100. 18 According to this previous study, FLI <30 could be used to rule out (sensitivity=87%) and

FLI ≥60 to rule in hepatic steatosis (specificity=86%) in an Italian population, thus, Bedogni et al suggested that the FLI was a simple and accurate predictor of hepatic steatosis. The validation of FLI in other populations has been evaluated in several studies,[19,20,42] and our present study also shows that NAFLD assessed by FLI is well-correlated with hepatic steatosis using abdominal ultrasonography in Chinese postmenopausal women. In the present study, it was showed that FLI was highly correlated with the various of obesity indices (data not shown), in addition, some previous studies reported that FLI was positively associated with homeostasis model assessment of insulin resistance and hs-CRP, and NAFLD assessed by FLI was an independent risk factor for hypertension and type 2 diabetes,[15,43] thus, all these findings may to some extend imply that FLI, representing NAFLD, is closely associated with metabolic syndrome.

It has been confirmed that central obesity is definitely associated with NAFLD. In subjects with central obesity, increased visceral adiposity results in the production of inflammatory adipokines and hormones, including tumor necrosis factor-α, interleukin-6, interleukin-1 and resistin and increased lipolysis and influx of free fatty acid to the liver, which eventrally leads to the synthesis of hepatic triglyceride.[44] Therefore, some studies evaluated the abilities of several obesity indices for predicting NAFLD.[16,17,19] A Korean study compared the abilities of WC and WHtR with those of DXA-measured trunk fat mass and CT-measured–visceral fat area for screening NAFLD, 16 and found that no significant differewnces were observed in the area ubder the curve values among these abdominal obesity indices in both men and women. Another Korean study in which FLI was also used to predict NAFLD showed that BMI, WC, and FLI were all useful index for predicting presence of NAFLD.[19] However, FLI is not superior to BMI and WC according to the area under ROC. A Chinese study, in which FLI was not involved, reported that WHR was superior to BMI, WC, and WHtR in prediction of NAFLD.[17] The present study showed that WHR and WC were the best indices for predicting the presence of NAFLD in postmenopausal women among the obestiy indices in addition to FLI. The difference between studies may be due to the different study designs, populations, and different age groups. The underlaying reasons are still needed to be explored.

Although obesity is a known risk factor for NAFLD, many recent studies have indicated that visceral fat accumulation may be a more important risk factor for NAFLD than simple obesity. Therefore, there is increased interest in identifying reliable methods for detecting body fat distribution.[45] VAI is a novel sex-specific index, based on WC, BMI, TG and HDL-c, indirectly expressing visceral adipose function. This index combined both anthropometric and metabolic variables to evaluate body fatness, and was used as a marker of both visceral fat

dysfunction and an individual's subsequent cardiometabolic risk. Several studies have evaluated the relationship between NAFLD and VAI, however, there is some controversy regarding the association between them. Some studies reported that VAI was closely associated with increased serum aminotransferase levels and incidence of NAFLD in patients with sleep apnea and could used as a diagnostic index for progressive liver histology and cardiovascular risk in NAFLD.[24,25] while the same observations were not obtained from other studies.[22,23] The present study showed that VAI was an useful index for predicting presence of NAFLD, however, it is not superior to any of obesity indices according to the area under ROC. The controversy among these studies may be due to the different populations or the relatively small sample size of each study. Therefore, further studies are needed.

Our study has several limitations. Firstly, we did not measure any inflammatory markers (such as monocyte chemo-tractant protein-1, interleukin-6, tumor necrosis factor-α and so on) and evaluate the level of insulin resistance. Secondly, we did not measure the blood estrogen level in each participant, thus, we could not provide any mechanistic explanation regarding our results. Thirdly, because all participants of this study, who were of Chinese ethnicity and were residents of Beijing, were enrolled in a single hospital and the sample size was relatively small, so our results cannot be extrapolated beyond this group. Finally, we did not perform a biopsy to define NAFLD, although ultrasonography is widely used in surveys of NAFLD.

Conclusions

FLI is closely associated with the presence of hepatic steatosis in Chinese postmenopausal women. Compared to the obesity indices frequently used, FLI is a better surrogate marker for predicting the presence of hepatic steatosis in Chinese postmenopausal women. FLI is simple to obtain and may help physicians select subjects for liver ultrasonography and can be employed for epidemiologic studies.

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AUTHOR DISCLOSURE

All the authors had full access to the data and participated in the conceptualization, design, and drafting of this manuscript. The authors report no conflict of interest.

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Table 1. Basic characteristics of the two groups. Data are expressed as mean (standard deviation) or number (%)

Variables	All women (n=680)	NAFLD group (n=227)	Control group (n=453)	*p*-value
Age, year	54.7 (4.1)	55.0 (6.3)	54.6 (4.3)	0.19
BMI, kg/m^2	24.0 (2.6)	25.6 (2.2)	23.2 (2.5)	<0.01
WC, cm	79.0 (5.4)	82.2 (4.4)	77.3 (5.0)	<0.01
WHR	0.84 (0.06)	0.88 (0.05)	0.83 (0.06)	<0.01
WHtR	0.49 (0.04)	0.52 (0.03)	0.48 (0.03)	<0.01
VAI	2.1 (1.6)	2.9 (2.0)	1.6 (1.1)	<0.01
FLI	21.3 (16.4)	34.3 (16.3)	14.8 (12.0)	<0.01
SBP, mmHg	119 (18)	126 (19)	115 (16)	<0.01
DBP, mmHg	70 (8)	73 (9)	70 (8)	<0.01
GGT,IU/L	19 (10)	24 (11)	17 (10)	<0.01
ALT,IU/L	19 (9)	22 (10)	17 (8)	<0.01
AST,IU/L	20 (5)	20 (6)	20 (5)	0.13
FBG, mmol/L	5.4 (1.1)	5.7 (1.4)	5.1 (0.7)	<0.01
TC, mmol/L	5.20 (0.91)	5.37 (0.87)	5.11 (0.91)	0.01
Triglyceride, mmol/L	1.41 (0.81)	1.85 (0.96)	1.18 (0.60)	<0.01
HDL-c, mmol/L	1.38 (0.31)	1.25 (0.26)	1.45 (0.32)	<0.01
LDL-c, mmol/L	3.23 (0.80)	3.41 (0.81)	3.14 (0.77)	<0.01
hs-CRP, mg/L	1.4 (1.7)	2.0 (2.0)	1.1 (1.5)	<0.01
Hypertension†	166 (24.4)	81 (35.7)	85 (18.8)	<0.01
Diabetes†	86 (12.6)	53 (26.6)	33 (7.3)	<0.01
Smoking status†				0.87
Nonsmoker	543 (79.9)	182 (80.2)	361 (79.7)	
Exsmoker	56 (8.2)	17 (7.5)	39 (8.6)	
Smoker	81 (11.9)	28 (12.3)	53 (11.7)	
Alcohol status†				0.02
Nondrinker	513 (75.4)	175 (77.1)	338 (74.6)	
Exdrinker	62 (9.1)	11 (4.8)	51 (11.3)	
Drinker	105 (15.4)	41 (18.1)	64 (14.1)	

BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; VAI: visceral adiposity index; FLI: fatty liver index; SBP: systolic blood pressure; DBP: diastolic blood pressure; GGT: γ-glutamyltransferase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; FBG: fasting blood glucose; TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein.
†by X^2 test.

Table 2. Adjusted odds ratio and 95% confidence interval (CI) for the presence of hepatic steatosis according to the corresponding cutoff values for the indices.

Variables	Cases	Total participants (n)	Prevalence (%)	OR† (95% CI)
Body mass index (kg/m^2)				
Normal	57	350	16.3	Reference
Overweight	135	271	49.8	3.55 (2.32-5.42)**
Obesity	40	59	67.8	5.81 (2.91-11.6)**
p for trend			<0.01	
Waist circumference (cm)				
Normal	67	393	17.0	Reference
High	160	287	55.7	3.86 (2.59-5.76)**
Waist-to-height ratio				
Normal	58	364	15.9	Reference
High	169	316	53.5	3.78 (2.53-5.65)**
Waist-to-hip ratio				
Normal	53	361	14.7	Reference
High	174	319	54.5	4.23 (2.81-6.37)**
Visceral adiposity index				
Quartile 1	18	200	9.0	Reference
Quartile 2	36	147	24.5	2.51 (1.27-4.98)*
Quartile 3	74	175	42.3	4.47 (2.36-8.49)**
Quartile 4	99	158	62.7	9.43 (4.97-17.9)**
p for trend			<0.01	
Fatty liver index				
<30	101	511	19.8	Reference
30-60	109	148	73.6	6.45 (3.99-10.4)**
>60	17	21	81.0	10.8 (3.19-36.9)**

†Adjusted for age, lifestyle variables, blood pressure, history of hypertension and diabetes, fasting blood glucose, total cholesterol, LDL-c and high sensitivity C-reactive protein.
*p<0.05; **p<0.01.

Table 3. Comparison of AUC and corresponding 95% confidence interval among the indices

Variables	Standard error	AUC (95% CI)	*p*-value
Body mass index (kg/m^2)	0.18	0.77 (0.73-0.80)	<0.01
Waist circumference (cm)	0.18	0.77 (0.74-0.81)	<0.01
Waist-to-hip ratio	0.18	0.77 (0.74-0.81)	<0.01
Waist-to-height ratio	0.18	0.77 (0.73-0.80)	<0.01
Visceral adiposity index	0.18	0.77 (0.73-0.81)	<0.01
Fatty liver index	0.15	0.85 (0.82-0.88)	<0.01

AUC: area under curve.

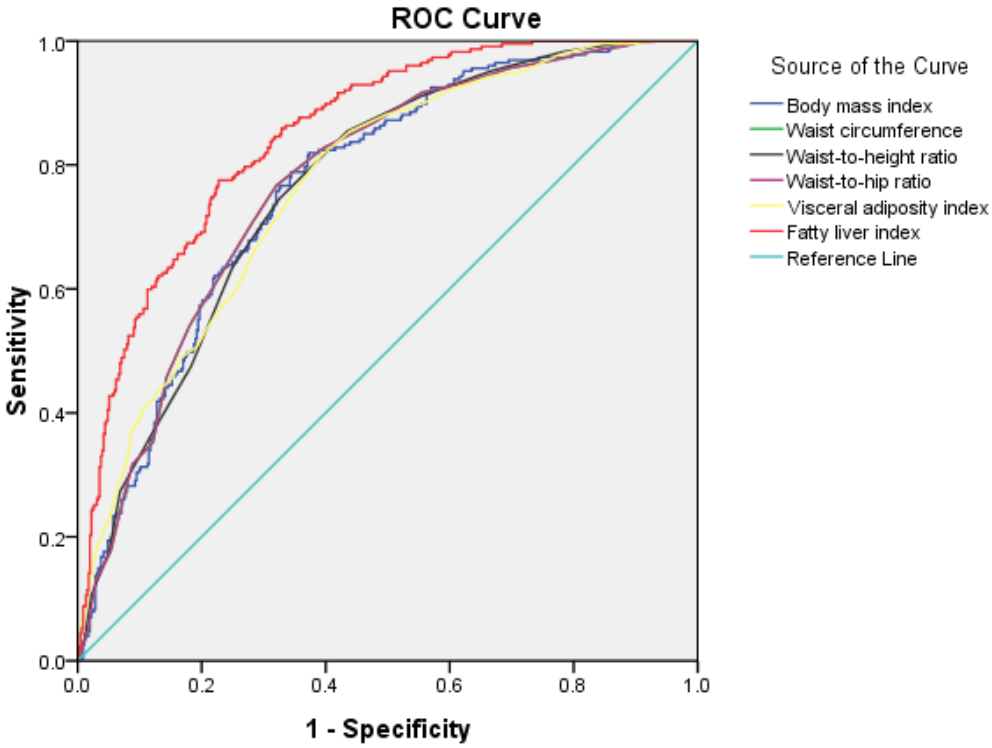

Figure 1. Receiver operating characteristic (ROC) curves of fatty liver index and obesity indices used to predict the presence of hepatic steatosis in postmenopausal women

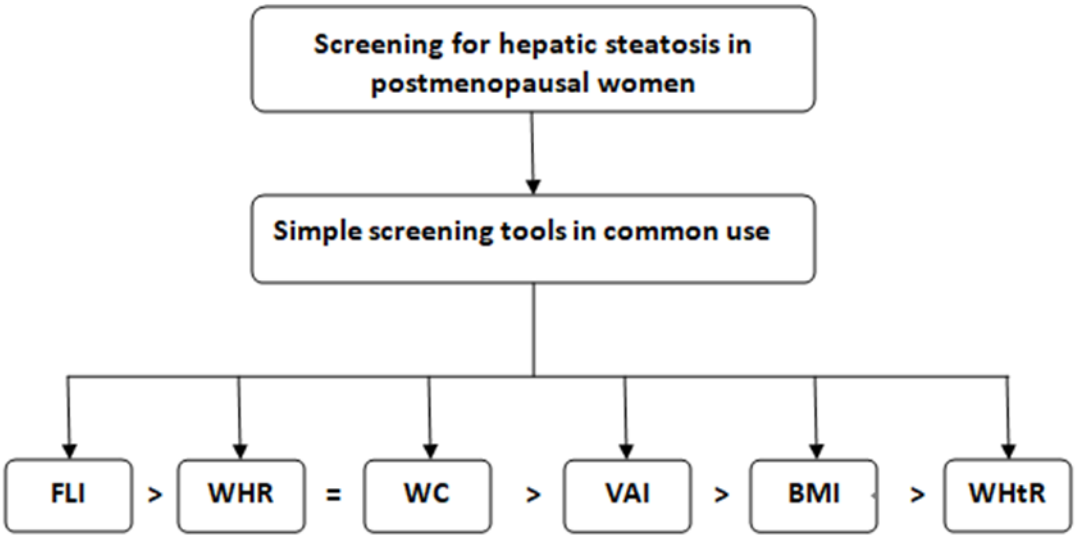

Figure 2. Predictive ability of commonly used screening indices for hepatic steatosis in postmenopausal women. FLI: fatty liver index; WHR: waist-to-hip ration; WC: waist circumference; VAI: visceral adiposity index; BMI: body mass index; WHtR: waist-to-height ratio.