Comparison of the ability between fatty liver index and triglyceride glucose index to screen hepatic steatosis in postmenopausal women: a cross-sectional study

CURRENT STATUS: POSTED

Peng Ju Liu
lpjjia@126.com Corresponding Author

Fang Ma
Peking Union Medical College Hospital

Yan Ning Zhu
Peking Union Medical College Hospital

Hui Ping Lou
Peking Union Medical College Hospital

DOI: 10.21203/rs.3.rs-20743/v1

SUBJECT AREAS
Endocrinology & Metabolism

KEYWORDS
Nonalcoholic fatty liver disease, Hepatic steatosis, Fatty liver index, triglyceride glucose index
Abstract
Background: To compare the potential of triglyceride glucose index (TyG) and fatty liver index (FLI) and to explore which index is better for detecting nonalcoholic fatty liver disease (NAFLD).

Methods: A cross-sectional study was conducted in 594 Chinese nondiabetic postmenopausal women retrospectively. NAFLD was defined as a hepatic steatosis observed on liver ultrasonography in the absence of a second cause. Binary Logistic regression model analysis was used to determine odds ratio (OR) and corresponding 95% confidence interval (CI) between hepatic steatosis and TyG as well as FLI. Receiver operating characteristic curve (ROC) and area under curve (AUC) were employed to determine the ability of FLI and TyG as well as the combination of TyG with obesity indices to detect hepatic steatosis, and the AUC values were also compared between them.

Results: women with the highest value of FLI or TyG had significantly higher odds of hepatic steatosis. The AUC values of FLI was significantly larger than that of TyG in either overall women (difference between area: 0.0743, 95% CI: 0.0396-0.109, P < 0.0001) or women younger (difference between area: 0.0629, 95% CI: 0.0262-0.0996, P=0.0008) and older (difference between area: 0.116, 95% CI: 0.0242-0.207, P=0.0132) than 60 years. Furthermore, when TyG was added to each obesity index, the AUC value of FLI was still significantly larger than that of each combination.

Conclusions: Compared with TyG along or combination of TyG and obesity indices, FLI is a better surrogate index for detecting hepatic steatosis among Chinese nondiabetic postmenopausal women.

Introduction
Nonalcoholic fatty liver disease (NAFLD) is used to describe a condition of triglyceride accumulation in the liver in the absence of excessive alcohol consumption and any other specific causes of hepatic steatosis, and it encompasses a wide spectrum of hepatic injuries ranging from simple nonalcoholic fatty liver disease (steatosis) to nonalcoholic steatohepatitis (NASH) which is characterized by liver inflammation with potential to progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma.

[1-3]. As the most common form of chronic liver disease, NAFLD affect 24–42% of people in Western countries and 5–40% in Asian countries [4-6]. In China, NAFLD has become one of the major causes of chronic liver disease, and the overall prevalence of NAFLD in Chinese adults has reached 20.1%
according to a recent meta-analysis [7]. NAFLD is frequently associated with visceral obesity, dyslipidemia, insulin resistance, as well as type 2 diabetes mellitus (T2DM) and may represent another component of metabolism syndrome (MetS), which is a well-known atherogenic condition [8]. Additionally, there is evidence that NAFLD might have a role in the development of T2DM and MetS rather than just being one of its manifestations [9]. Further, individuals with NAFLD are at significantly higher risk of cardiovascular disease [10–13], and those with evidence of NASH and advanced fibrosis are at markedly increased risk of adverse outcomes including overall mortality, and liver-specific morbidity and mortality, respectively [14]. Therefore, NAFLD is becoming an increasingly important health issue worldwide.

In women, it seems that the prevalence of hepatic steatosis can be affected by menopausal status [15–17]. A study reported that the prevalence of NAFLD in women was lower before menopause but was higher after menopause than that in men [18], 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 [19]. Another point worth noting is that postmenopausal women accumulate more fat tissue in the intra-abdominal region than do premenopausal women and subsequently have a greater risk of developing metabolic disorders [20], which may make postmenopausal women more likely to develop hepatic steatosis. Therefore, it is very important to explore a simple as well as effective method to screen hepatic steatosis in population of postmenopausal women.

The gold standard for diagnosis and quantification of hepatic fibrosis in individuals with NAFLD is liver biopsy. However, this method has limited diagnostic value in a population-based study due to its invasive nature [21]. For this reason, non-invasive methods are preferred as first line investigations. In clinical settings, an abdominal ultrasonography is the most common technique used to assess the presence of NAFLD. However, abdominal ultrasonography is also laborious for study participants. Since hepatic steatosis is closely associated with obesity as well as metabolic disorders, a number of studies have been conducted in order to find simple and efficient markers to screen hepatic steatosis. These markers often include anthropometric indices [22–24], serum lipid-associated indices [25, 26],
aminotransferases [27], or the markers composed of them. Bedogni et al. developed a simple scoring system called the fatty liver index (FLI) as a predictor of fatty liver disease [28], and several studies have reported that NAFLD assessed by FLI was well-correlated with hepatic steatosis using abdominal ultrasonography in a general population [29, 30]. In one of our previous studies, we have identified that FLI is a better marker for predicting the presence of hepatic steatosis in postmenopausal women as compared with several obesity indices including body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), and visceral adiposity index [31]. Recently, there is growing interest in the triglyceride glucose index (TyG). A large observational study from China has reported that TyG is effective to identify individuals at risk for NAFLD, especially when combining it to alanine aminotransferase (ALT) [32]. In addition, several studies have determined that TyG is a surrogate for identifying insulin resistance [33, 34], which is closely linked with hepatic steatosis. However, between FLI and TyG, it is still unclear which index is better for detecting of hepatic steatosis among a population of postmenopausal women. Therefore, we conducted this study to investigate their potential to detect hepatic steatosis, using the data from one of our previous studies [31], from which women without diabetes were selected as a nondiabetic population in this study.

Methods

Participants

This was a retrospective study involving 594 postmenopausal women who had previously been recruited in one of our previous studies, from July to September 2016. Those women 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. A standard questionnaire was used by trained physicians to collect information of the participants, including age, lifestyle factors (smoking and drinking status), medical history, medication use and duration of menopause. The exclusion criteria have been well described in one of our previous studies [31]. Based on the previous study, we further excluded individuals with diabetes in this study in order to avoid the potential effects of diabetes on the serum lipids and fasting plasma glucose, if that actually
happens, the values of TyG would be greatly affected. All participants were naturally postmenopausal women who had amenorrhea for at least 12 months after their final menstruation and did not have any pathological cause of amenorrhea [35,36].

**Measurements**

Anthropometric measurements of individuals wearing light clothing and without shoes were conducted by well-trained examiners. Height was measured to the nearest 0.1cm with a portable stadiometer. Weight was measured in an upright position to the nearest 0.1kg with a calibrated scale. BMI was calculated by dividing weight (kg) by height squared (m²). WC measurements were taken at the end of normal expiration to the nearest 0.1cm, 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.

All participants underwent venous blood collection in the morning after fasting for 10-12 hours to determine concentrations of total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), fasting plasma glucose (FPG), high sensitivity C-reactive protein (hs-CRP), ALT, aspartate aminotransferase (AST), and γ-glutamyltransferase (γ-GGT), using an automated analyzer (Olympus AU5800, Japan).

**Evaluation criteria**

The FLI was calculated according to a previously published report by Bedogni et al.:[28]

\[
[ e^{0.953 \times \log(TG) + 0.139 \times BMI + 0.718 \times \log e(GGT) + 0.053 \times \text{waist circumference}-15.745] / [1+e^{0.953 \times \log(TG) + 0.139 \times BMI + 0.718 \times \log e(GGT) + 0.053 \times \text{waist circumference}-15.745}] \times 100,
\]

with TGs 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).

TyG was calculated as: TyG = Ln [TG (mg/dl) FPG (mg/dl)/2] [34]. To date, there is no recommended cut-off value of TyG to detect hepatic steatosis, thus values of TyG were divided into quartiles (quartile 1, < 8.1; quartile 2, 8.1-8.5; quartile 3, 8.5-8.8; quartile 4, ≥ 8.8) according to its respective cut-off points of entire distribution for this study population.
BMI was divided into three groups, normal (< 24.0 kg/m²), overweight (24.0-27.9 kg/m²), and obesity (≥ 28.0 kg/m²) [37]. A WHtR of ≥ 0.50 or a WHR of ≥ 0.85 was defined as a central obesity [38-40].

**Ultrasonography for liver and criteria of NAFLD**

NAFLD was defined as the presence of definite hepatic steatosis on ultrasonography, such as a bright hepatic echo pattern, increased attenuation of the echo beam and loss of intrahepatic architectural detail without a secondary cause [41,42]. Ultrasonography of the liver was performed using a 3.5-MHz convex-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 16.0, 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. Binary logistic regression analyses were used to determine the odds ratio (ORs) and 95% confidence interval (CI) of hepatic steatosis according to the classifications of TyG as well as FLI with adjustment for potential confounders. Receiving-operating characteristic (ROC) curves and area under the curve (AUC) were employed to calculate the AUC values of FLI, TyG as well as combination of TyG with each obesity index to detect hepatic steatosis. Comparisons between the AUC of FLI and TyG, as well as TyG plus each obesity index (BMI, WHR, or WHtR) were conducted by the method described by DeLong [43].

**Results**

**The basic characteristics of participants with and without NAFLD**

Of the 594 postmenopausal women, 29.3% (n = 174) were detected in the presence of hepatic steatosis by ultrasonography. Compared with women without hepatic steatosis, women with hepatic steatosis had significantly higher age, BMI, WC, WHR, WHtR, FLI, TyG, SBP, DBP, GGT, ALT, FPG, TC, TG, LDL-c, hs-CRP, and prevalence of hypertension, but lower HDL-c (all $P \leq 0.001$). There were no significant differences in the concentration of AST between the two groups (Table 1).
Table 1
The basic characteristics between two groups

| Variables                  | All (n = 594) | NAFLD (n = 174) | Non-NAFLD (n = 420) | P value |
|----------------------------|---------------|-----------------|--------------------|---------|
| Age (year)                 | 54.4(6.7)     | 56.5(6.1)       | 53.5(6.8)          | < 0.001 |
| BMI (kg/m²)                | 23.8(2.6)     | 25.5(2.1)       | 23.2(2.5)          | < 0.001 |
| Waist circumference (cm)   | 78.6(5.4)     | 82.0(4.3)       | 77.2(5.0)          | < 0.001 |
| Waist-to-height ratio      | 0.49(0.04)    | 0.51(0.03)      | 0.48(0.03)         | < 0.001 |
| Waist-to-hip ratio         | 0.84(0.06)    | 0.88(0.05)      | 0.83(0.05)         | < 0.001 |
| Fatty liver index          | 19.9(15.6)    | 32.5(16.0)      | 14.7(12.1)         | < 0.001 |
| TyG                        | 8.5(0.5)      | 8.8(0.5)        | 8.3(0.5)           | < 0.001 |
| SBP (mmHg)                 | 117(17)       | 123(18)         | 114(16)            | < 0.001 |
| DBP (mmHg)                 | 71(8)         | 73(9)           | 70(8)              | < 0.001 |
| GGT (IU/L)                 | 19(10)        | 23(10)          | 17(10)             | < 0.001 |
| ALT (IU/L)                 | 19(9)         | 22(10)          | 17(8)              | < 0.001 |
| AST (IU/L)                 | 20(5)         | 20(6)           | 20(5)              | 0.270   |
| FPG (mmol/L)               | 5.1(0.4)      | 5.2(0.4)        | 5.0(0.4)           | < 0.001 |
| Total cholesterol (mmol/L) | 5.19(0.87)    | 5.38(0.81)      | 5.12(0.89)         | 0.001   |
| Triglyceride (mmol/L)      | 1.35(0.77)    | 1.79(0.93)      | 1.16(0.60)         | < 0.001 |
| HDL-cholesterol (mmol/L)   | 1.40(0.31)    | 1.27(0.25)      | 1.45(0.32)         | < 0.001 |
| LDL-cholesterol (mmol/L)   | 3.22(0.77)    | 3.43(0.77)      | 3.14(0.75)         | < 0.001 |
| hs-CRP (mg/L)              | 1.3(1.6)      | 1.8(1.8)        | 1.1(1.4)           | < 0.001 |
| Hypertension               | 21.0(125)     | 31.0(54)        | 16.9(71)           | < 0.001 |
| Smoking status             |               |                 |                    | 0.853   |
| Nonsmoker                  | 80.8(480)     | 82.2(143)       | 80.2(337)          |        |
| Exsmoker                   | 8.3(49)       | 7.5(13)         | 8.6(36)            |        |
| Smoker                     | 10.9(65)      | 10.3(18)        | 11.2(47)           |        |
| Alcohol consumption status |               |                 |                    | 0.121   |
| Nondrinker                 | 76.4(454)     | 79.3(138)       | 75.2(316)          |        |
| Exdrinker                  | 9.6(57)       | 5.8(10)         | 11.2(47)           |        |
| Drinker                    | 14.0(83)      | 14.9(26)        | 13.6(57)           |        |

BMI, body mass index; FLI, fatty liver index; TyG, triglyceride glucose index; SBP, systolic blood pressure; DBP, diastolic blood pressure; γ-GGT, γ-glutamyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FPG, fasting plasma glucose; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein

Associations between the presence of hepatic steatosis and the classifications of FLI and TyG

The lowest values of FLI and TyG were used as the reference, respectively. For FLI, compared with women with the lowest level (< 30), women with the upper two levels had significantly higher odds of hepatic steatosis (all P < 0.01) after adjusting for age, lifestyle factors (smoking and drinking status), blood pressure, history of hypertension, TC, HDL-c, LDL-c, ALT, AST, FPG, and hs-CRP (Table 2).
Table 2
Odds ratio and 95% confidence interval (CI) for the presence of hepatic steatosis according to the respective cutoff values for fatty liver index and triglyceride glucose index.

| Variables                      | Cases (n) | Total participants (n) | Prevalence (%) | OR (95% CI) |
|-------------------------------|-----------|------------------------|----------------|-------------|
| **Triglyceride glucose index**|           |                        |                |             |
| Quartile 1                    | 11        | 148                    | 7.4            | reference   |
| Quartile 2                    | 28        | 149                    | 18.8           | 1.889(0.819–4.360) |
| Quartile 3                    | 54        | 149                    | 36.2           | 2.848(1.236–6.562)* |
| Quartile 4                    | 81        | 148                    | 54.7           | 5.299(2.073–13.547)** |
| P for trend                   |           |                        |                | <0.001      |
| **Fatty liver index**         |           |                        |                |             |
| <30                           | 90        | 472                    | 19.1           | reference   |
| 30–60                         | 74        | 108                    | 68.5           | 5.156(3.070–8.659)** |
| >60                           | 10        | 14                     | 71.4           | 8.095(2.192–29.891)** |
| P for trend                   |           |                        |                | <0.001      |

*P < 0.05; **P < 0.01

As for TyG, women in the third and highest quartiles had significant higher odds of hepatic steatosis (all P < 0.05) than women in the lowest quartile, with adjustments for age, BMI, WC, lifestyle factors (smoking and drinking status), blood pressure, history of hypertension, TC, LDL-c, HDL-c, ALT, AST, GGT, and hs-CRP (Table 2).

ROC curve analyses of the two indicators of hepatic steatosis and comparison of AUC values between FLI and TyG as well as TyG plus each obesity index

The AUC values and the 95% CI for detecting the presence of hepatic steatosis by FLI and TyG are shown in Table 3. Both FLI and TyG showed significant areas under the ROC curve in women under or over 60 years of age or in overall women (Fig. 1, 2, and 3).
| Variables                  | Standard error | AUC (95% CI)        | p-value  |
|----------------------------|----------------|---------------------|----------|
| Women with Age < 60 years  |                |                     |          |
| Triglyceride glucose index | 0.023          | 0.779 (0.734–0.823) | < 0.001  |
| Fatty liver index          | 0.019          | 0.842 (0.805–0.878) | < 0.001  |
| Women with Age ≥ 60 years  |                |                     |          |
| Triglyceride glucose index | 0.049          | 0.680 (0.584–0.775) | < 0.001  |
| Fatty liver index          | 0.040          | 0.795 (0.718–0.873) | < 0.001  |
| Overall (n = 594)          |                |                     |          |
| Fatty liver index          | 0.017          | 0.836 (0.803–0.868) | < 0.001  |
| Triglyceride glucose index | 0.020          | 0.764 (0.724–0.804) | < 0.001  |
| Triglyceride glucose index + BMI | 0.020  | 0.780 (0.741–0.819) | < 0.001  |
| Triglyceride glucose index + WHtR | 0.020 | 0.776 (0.737–0.815) | < 0.001  |
| Triglyceride glucose index + WHR | 0.020  | 0.778 (0.738–0.817) | < 0.001  |

AUC, area under the curve; CI, confidence interval; BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio

In overall women, the AUC values of FLI and TyG to detect hepatic steatosis were 0.836 (95% CI: 0.803–0.868, P < 0.001) and 0.764 (95% CI: 0.724–0.804, P < 0.001), respectively (Table 3 and Fig. 1). For women younger than 60 years, the AUC values of FLI and TyG were 0.842 (95% CI: 0.805–0.878, P < 0.001) and 0.779 (95% CI: 0.734–0.823, P < 0.001) (Table 3 and Fig. 2); for women older than 60 years, they were 0.795 (95% CI: 0.718–0.873, P < 0.001) and 0.680 (95% CI: 0.584–0.775, P < 0.001) (Table 3 and Fig. 3), respectively. Moreover, the differences in AUC values between the two indices were also compared. According to the method by DeLong [43], the AUC value of FLI was significantly larger than that of TyG in either overall women (difference between area: 0.0743, 95% CI: 0.0396–0.109, P < 0.0001) or women younger (difference between area: 0.0629, 95% CI: 0.0262–0.0996, P = 0.0008) or older (difference between area: 0.116, 95% CI: 0.0242–0.207, P = 0.0132) than 60 years (Table 4). Furthermore, the comparison of the AUC between FLI and combination TyG with each obesity index was also conducted. When TyG was added to BMI, WHR, or WHtR, although the combined AUC of TyG plus each obesity index was slightly higher than that of TyG alone (Table 3 and Fig. 4), the AUC value of FLI was still significantly larger than that of each combination (Table 4 and Fig. 4). (The ROC curves, sensitivity, specificity, as well as the AUC values of BMI, WC, WHR, and WHtR, TyG, and FLI for detecting hepatic steatosis are shown in Supplemental Table and Supplemental Figure)
Table 4
Comparison of the AUC values between FLI and TyG along as well as combination TyG with obesity indices for detecting hepatic steatosis

|                          | Difference between area (95% CI) | P-value  |
|--------------------------|----------------------------------|----------|
| FLI vs. TyG along        |                                  |          |
| Overall women            | 0.0743 (0.0396–0.109)            | < 0.0001 |
| Women < 60 years         | 0.0629 (0.0262–0.0996)           | 0.0008   |
| Women ≥ 60 years         | 0.116 (0.0242–0.207)             | 0.0132   |
| FLI vs. (TyG + BMI)      | 0.0560 (0.0263–0.0857)           | 0.0002   |
| FLI vs. (TyG + WHR)      | 0.0581 (0.0276–0.0886)           | 0.0002   |
| FLI vs. (TyG + WHtR)     | 0.0595 (0.0297–0.0894)           | 0.0001   |

AUC, area under the curve; FLI, fatty liver index; TyG, triglyceride glucose index; BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio

Discussion
To the best of our knowledge, this study is the first study to compare the discriminatory potentials of fatty liver index (FLI) and triglyceride glucose index (TyG) for detecting hepatic steatosis in Chinese nondiabetic postmenopausal women. In this study, we found that both FLI and TyG had the significantly higher odds ratio for hepatic steatosis than their respective reference after adjusting for the potential confounders. Moreover, we also found that FLI is a superior surrogate index than TyG for detecting the presence of hepatic steatosis in Chinese nondiabetic postmenopausal women.

Furthermore, when TyG was added to each obesity index, the superiority of FLI over each combination is still significant. In conjunction with our previous findings [31], where we have identified that FLI is a better marker for predicting the presence of hepatic steatosis in postmenopausal women compared with several obesity indices including BMI, WC, WHR, WHtR, and visceral adiposity index, it seems that FLI may be the first choice when screening for hepatic steatosis in Chinese nondiabetic postmenopausal women.

Globally, the prevalence of NAFLD is estimated to be about 25% and often accompanies an increased prevalence of overweight or obesity [44]. With the introduction of westernized lifestyle and increasing frequency of obesity in the Asia-Pacific region including China, the prevalence of NAFLD has increased rapidly over the past two decades [7, 45, 46]. In this study, the prevalence of NAFLD was 29.3%, which is slightly higher than the result of a recent meta-analysis where the overall prevalence of NAFLD in Chinese adults was reported to be 20.1%. The explanation might be due to the different study population. However, the prevalence in this study is slightly lower than the result of one of our previous studies in which the prevalence of hepatic steatosis was 33.4% [31]. That is because we
have excluded women with a history of T2DM or who were highly suspected of diabetes based on the results of physical examination, since NAFLD is closely associated with diabetes.

For women after menopause, fat distribution shifts from gluteofemoral subcutaneous adipose tissue (SAT) to abdominal visceral adipose tissue (VAT) [47]. It has been reported that significant increases in VAT only occur in those women who become postmenopausal during a four-year follow-up [48]. As a result, it is that the decrease of SAT as well as the increase of VAT makes postmenopausal women more prone to cardiometabolic disorders as compared with premenopausal women. Wong et al. reported that the prevalence of NAFLD was about two times higher in men compared with in women, but the prevalence of NAFLD in women increased with age and, in those older than 50 years, the prevalence of NAFLD became similar and even higher than that in men [49]. Considering that the average age of menopause is approximately 50 years, the assumption that menopause itself might affect metabolic changes and increase the development of NAFLD can be supposed [24].

It has been confirmed that there are close links between fatty liver and underlying insulin resistance, metabolic syndrome, T2DM, cardiovascular damage as well as cardiovascular events. Moreover, 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 [50]. A very recent review has demonstrated that individuals with evidence of NASH and advanced fibrosis are at markedly increased risk of adverse outcomes including overall mortality, and liver-specific morbidity and mortality, respectively [14]. Therefore, NAFLD has been becoming an increasingly recognized public health problem. In order to facilitate the screening of NAFLD in the population, a number of studies have been conducted with attempt to explore not only simple but also accurate markers. It has been confirmed that central obesity is definitely associated with NAFLD. In individuals with central obesity, an increased VAT results in an excessive production of inflammatory adipokines and hormones in conjunction with an increased lipolysis and influx of free fatty acid to the liver, which eventually leads to the synthesis of hepatic TG [51]. Therefore, obesity indices are frequently used in the screening of NAFLD [22–24]. According to Yoo et al., WC and WHtR were found to be as useful as dual-energy X-ray absorptiometry (DXA) and computed tomography (CT) for predicting NAFLD in adults aged 20–
88 years [22]. Recently, Hong et al. have reported that WHR is a more accurate indicator for NAFLD than BMI and WC in postmenopausal women [24]. The possible explanation may be that WHR reflects the assumption ratio of abdominal VAT to gluteofemoral SAT, and it has been reported that the ratio of VAT to SAT is independently associated with the clustering of multiple cardiometabolic risk factors in women but not in men [52]. Further, because the hormone changes after menopause causes the deposition of abdominal VAT from the femoral SAT, the clinical significance of WHR might be more distinct after menopause [48]. Also, one of our previous studies showed that, among the indicators of central obesity, WHR is the best predictive marker for MetS development in Chinese postmenopausal women [40].

In addition to obesity indicators, the associations of other markers with NAFLD have been also investigated. Previously, we reported a index termed fatty liver index (FLI), which is an index firstly reported by Bedogni et al. and its score ranges from 0 to 100 [28]. A FLI of < 30 could be used to rule out (sensitivity = 87%) and a FLI of ≥ 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 general populations has been confirmed in several studies [29, 30], and our previous study also showed that NAFLD assessed by FLI is well-correlated with hepatic steatosis using abdominal ultrasonography in Chinese postmenopausal women [31]. Unfortunately, there are few similar reports on the use of FLI to screen NAFLD in postmenopausal women other than our report, in which we compared the FLI and several frequently used obesity indices and found that FLI is generally better than indices including BMI, WC, WHR, WHtR, as well as visceral adiposity index in detecting hepatic steatosis in postmenopausal women.

NAFLD is considered as the liver manifestation of MetS and the two key components of MetS, triglyceride (TG) and fasting plasma glucose (FPG) are overproduced by the fatty liver [53]. Recently, the triglyceride glucose index (TyG) has been recommended as a reliable and simple surrogate marker for insulin resistance [33, 34, 54]. The close association between the TyG and liver steatosis has been demonstrated in people from Mexico and China [32, 55]. The explanation may be that TyG is a specific indicator of hepatic insulin resistance since it is well correlated with the amount of
hepatic fat [32], whose amount predicts mortality and development of T2DM in individuals with NAFLD [56]. In addition, several studies have found that triglyceride to high-density lipoprotein cholesterol ratio is independently associated with NAFLD as well as the severity of NAFLD [25, 26]. However, there are sparse studies specifically examining the association between TyG and hepatic steatosis among postmenopausal women.

In our present study, we firstly reported the comparison of the potential between FLI and TyG to detect hepatic steatosis in a population of menopausal women, and found that FLI is superior to TyG among postmenopausal women. After grouping by age, the superiority of FLI over TyG is unchanged. Unlike FLI, the TyG index does not contain variables that directly reflect body weight or body shape, although both FLI and TyG contain TG within them. Therefore, we further added obesity indices including BMI, WHR, or WHtR to the TyG to observe their combined effects to detect hepatic steatosis. Although the combined AUC of TyG plus each obesity index was slightly higher than that of TyG alone, the AUC value of FLI was still significantly larger than that of each combination, suggesting that FLI is a superior indicator for screening hepatic steatosis among postmenopausal women in a population-based study.

Strengths and limitations

This study firstly compares the differences in the ability to detect hepatic steatosis between FLI and TyG as well as the combination of TyG and obesity indices among postmenopausal women, and confirms that FLI is a superior indicator over TyG along or the combination of TyG and frequently used obesity indices. In addition, we only recruited relatively healthy women without diabetes, which avoids the potential influence of diabetes on metabolisms of the participants. Furthermore, we not only calculated the AUC values of FLI and TyG, but also compared the differences between them statistically, which enhances convincingness of our data. On the other side, the current study has several limitations. Its cross-sectional design makes it difficult to assess causal relationship. Also, we did not evaluate the level of insulin resistance as well as the blood estrogen level in each participant, thus, we could not provide any mechanistic explanation regarding our results. In addition, 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. Further, ultrasonography as a modality for detecting NAFLD is not the gold standard for the diagnosis of NAFLD, but is generally regarded as a fairly noninvasive and reliable modality for the diagnosis of hepatic steatosis, with a known sensitivity of 85% and specificity of 94% [57]. Finally, we were unable to collected detailed data about diet and physical activity and so on.

Conclusions
In a population-based study involving the screening of NAFLD in postmenopausal women, FLI is a better surrogate marker for predicting the presence of hepatic steatosis as compared with TyG index.

Declarations
Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: This study was not supported by any fund.

Ethical statement
This study was approved by the Ethics Committee of Peking Union Medical College Hospital, China Academic Medical Science. This study was conducted in accordance with both the Declaration of Helsinki of 1975, as revised in 1983, and guidelines of the center’s institutional review board. All participants had provided written informed consent in the previous study.

Acknowledgement: We thank all the participants of the study.

We have reviewed the final version of the manuscript and approve it for publication

Contribution to authorship: Liu PJ and Ma F designed the study and managed the data. Liu PJ reviewed and revised the manuscript critically. Zhu YN and Liu PJ were responsible for quality assurance and data analysis. Lou HP collected the data. All authors read and approve the final manuscript.

Availability of data and materials: a subgroup analysis of the data of Asia Pac J Clin Nutr 2019;28:23-30

References
1. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;346:122–31.
2. Yang Z, Wang X, Wen J, Ye Z, Li Q, He M, et al. Prevalence of non-alcoholic fatty liver disease and its relation to hypoadiponectinaemia in the middle-aged and elderly
Chinese population. Arch Med Sci. 2011;7:665–72.

3. Tariq R, Axley P, Singal AK. Extra-Hepatic Manifestations of Nonalcoholic Fatty Liver Disease: A Review. J Clin Exp Hepatol. 2020;10:81–7.

4. Fan JG, Saibara T, Chitturi S, Kim BI, Sung JJ, Chutaputti A. What are the risk factors and settings for non-alcoholic fatty liver disease in Asia-Pacific? J Gastroenterol Hepatol. 2007;22:794–800.

5. Amarapurkar DN, Hashimoto E, Lesmana LA, Sollano JD, Chen PJ, Goh KL. How common is non-alcoholic fatty liver disease in the Asia-Pacific region and are there local differences? J Gastroenterol Hepatol. 2007;22:788–93.

6. Caballeria L, Auladell MA, Toran P, Miranda D, Aznar J, Pera G, et al. Prevalence and factors associated with the presence of non alcoholic fatty liver disease in an apparently healthy adult population in primary care units. BMC Gastroenterol. 2007;7:41.

7. Li Z, Xue J, Chen P, Chen L, Yan S, Liu L. Prevalence of nonalcoholic fatty liver disease in mainland of China: A meta-analysis of published studies. J Gastroenterol Hepatol. 2014;29:42–51.

8. Caballería L, Pera G, Auladell MA, Torán P, Muñoz L, Miranda D, et al. Prevalence and factors associated with the presence of nonalcoholic fatty liver disease in an adult population in Spain. Eur J Gastroenterol Hepatol. 2010;22:24–32.

9. Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol. 2015;62:47–64.

10. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. New Engl J Med. 2010;363:1341–50.

11. Bhatia LS, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? Eur Heart J. 2012;33:1190-200.

12. Stahl EP, Dhindsa DS, Lee SK, Sandesara PB, Chalasani NP, Sperling LS. Nonalcoholic
fatty liver disease and the heart: JACC state-of-the-art review. J Am Coll Cardiol. 2019;73:948–63.

13. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: a meta-analysis. J Hepatol. 2016;65:589–600.

14. Cotter TG, Rinella MNAFLD. 2020: The State of the Disease. Gastroenterology 2020. pii: S0016-5085(20)30223-7(in press).

15. Volzke H, Schwarz S, Baumeister SE, Wallaschofski H, Schwahn C, Grabe HJ, et al. Menopausal status and hepatic steatosis in a general female population. Gut. 2007;56:594–5.

16. Moon SS. Relationship between serum uric acid level and nonalcoholic fatty liver disease in pre- and postmenopausal women. Ann Nutr Metab. 2013;62:158–63.

17. Venetsanaki V, Polyzos SA. Menopause and Non-Alcoholic Fatty Liver Disease: A review focusing on therapeutic perspectives. Curr Vasc Pharmacol. 2019;17:546–55.

18. Park SH, Jeon WK, Kim SH, Kim HJ, Park DI, Cho YK, et al. Prevalence and risk factors of non-alcoholic fatty liver disease among Korean adults. J Gastroenterol Hepatol. 2006;21:138–43.

19. Suzuki A, Abdelmalek MF. Nonalcoholic fatty liver disease in women. Womens Health (Lond Engl). 2009;5:191-203.

20. Shi H, Cleqq DJ. Sex differences in the regulation of body weight. Physiol Behav. 2009;97:199-204.

21. Gilmore IT, Burroughs A, Murray-Lyon IM, Williams R, Jenkins D, Hopkins A. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. Gut. 1995;36:437-41.
22. Yoo HJ, Park MS, Lee CH, Yang SJ, Kim TN, Lim KI, et al. Cutoff points of abdominal obesity indices in screening for nonalcoholic fatty liver disease in Asians. Liver Int. 2010;30:189-96.

23. Zheng RD, Chen ZR, Chen JN, Lu YH, Chen J. Role of body mass index, waist-to-height and waist-to-hip ratio in prediction of Nonalcoholic fatty liver disease. Gastroenterol Res Pract. 2012;2012:362147.

24. Hong SH, Hwang SY, Kim JA, Lee YB, Roh E, Kim NH, et al. Comparison of anthropometric indices for the screening of nonalcoholic fatty liver disease in pre- and postmenopausal women. Menopause. 2020;27:88-94.

25. Wu KT, Kuo PL, Su SB, Chen YY, Yeh ML, Huang CI, et al. Nonalcoholic fatty liver disease severity is associated with the ratios of total cholesterol and triglycerides to high-density lipoprotein cholesterol. J Clin Lipidol 2016;10:420-5.e1.

26. Fukuda Y, Hashimoto Y, Hamaguchi M, Fukuda T, Nakamura N, Ohbora A, et al. Triglycerides to high-density lipoprotein cholesterol ratio is an independent predictor of incident fatty liver; a population-based cohort study. Liver Int. 2016;36:713-20.

27. Lu CW, Lin MS, Lin YS, Chang IJ, Tsai MH, Wei KL, et al. Aminotransferase ratio is a useful index for hepatosteatosis in children and adolescents: a cross-sectional observational Study. Gastroenterol Nurs. 2019;42:486-95.

28. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC gastroenterol. 2006;6:33.

29. Kim JH, Kwon SY, Lee SW, Lee CH. Validation of fatty liver index and lipid accumulation product for predicting fatty liver in Korean population. Liver int. 2011;31:1600-1.

30. Zelber-Sagi S, Webb M, Assy N, Blendis L, Yeshua H, Leshno M, et al. Comparison of
fatty liver index with noninvasive methods for steatosis detection and quantification. 
World J gastroenterol. 2013;19:57–64.

31. Liu PJ, Ma F, Zhu YN, Lou HP. Utility of different indices in screening Chinese 
postmenopausal women for hepatic steatosis. Asia Pac J Clin Nutr. 2019;28:23–30.

32. Zhang S, Du T, Zhang J, Lu H, Lin X, Xie J, et al. The triglyceride and glucose index 
(TyG) is an effective biomarker to identify nonalcoholic fatty liver disease. Lipids 
Health Dis. 2017;16:15.

33. Won KB, Park GM, Lee SE, Cho IJ, Kim HC, Lee BK, et al. Relationship of insulin 
resistance estimated by triglyceride glucose index to arterial stiffness. Lipids Health 
Dis. 2018;17:268.

34. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting 
glucose and triglycerides as surrogate for identifying insulin resistance in apparently 
healthy subjects. Metab Syndr Relat Disord. 2008;6:299–304.

35. Den Tonkelaar I, Broekmans FJ, De Boer EJ, Te Velde ER, Soules MR, Parrott E, et al. 
The Stages of Reproductive Aging Workshop. Menopause. 2002;9:463–65.

36. Utian WH. The International Menopause Society menopause-related terminology 
definitions. Climacteric. 1999;2:284–86.

37. Cooperative Mata-analysis Group of China Obesity Task Force. Predictive values of 
body mass index and waist circumference to risk factors of related diseases in 
Chinese adult population [Article in Chinese]. Zhonghua Liu Xing Bing Xue Za Zhi. 
2002;23:5–10.

38. Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a 
screening tool for the prediction of cardiovascular disease and diabetes: 0.5 could be 
a suitable global boundary value. Nutr Res Rev. 2010;23:247–69.

39. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than
waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. Obes Rev. 2012;13:275–86.

40. Liu PJ, Ma F, Lou HP, Zhu YN. Utility of obesity indices in screening Chinese postmenopausal women for metabolic syndrome. Menopause. 2014;21:509–14.

41. Sanyal AJ. AGA technical review on nonalcoholic fatty liver disease. Gastroenterology. 2002;123:1705–25.

42. Joy D, Thava VR, Scott BB. Diagnosis of fatty liver disease: is biopsy necessary? Eur J Gastroenterol Hepatol. 2003;15:539–43.

43. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;8:37–45.

44. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64:73–84.

45. Farrell GC, Chitturi S, Lau GKK, Sollano J. the Asia-Pacific Working Party on NAFLD. Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region. Executive summary. J Gastroenterol Hepatol. 2007;22:775–7.

46. Chitturi S, Wong VW, Farrell G. Nonalcoholic fatty liver in Asia: firmly entrenched and rapidly gaining ground. J Gastroenterol Hepatol. 2011;26(Suppl. 1):163–72.

47. Abdulnour J, Doucet E, Brochu M, Lavoie JM, Strychar I, Rabasa-Lhoret R, et al. The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa New Emerging Team group study. Menopause (New York NY). 2012;19:760–67.

48. Lovejoy JC, Champagne CM, De Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (Lond).
2008;32:949-58.

49. Wong VW, Chu WC, Wong GL, Chan RS, Chim AM, Ong A, et al. Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. Gut. 2012;61:409-15.

50. Zelber-Sagi S, Nitzan-Kaluski D, Halpern Z, Oran R. Prevalence of primary non-alcoholic fatty liver disease in a population-based study and its association with biochemical and anthropometric measures. Liver Int. 2006;26:856-63.

51. Krawczyk M, Bonfrate L, Portincasa P. Nonalcoholic fatty liver disease. Best Pract Res Clin Gastroenterol. 2010;24:695-708.

52. He H, Ni Y, Chen J, Zhao Z, Zhong J, Liu D, et al. Sex difference in cardiometabolic risk profile and adiponectin expression in subjects with visceral fat obesity. Transl Res. 2010;155:71-7.

53. Adiels M, Westerbacka J, Soro-Paavonen A, Hakkinen AM, Vehkavaara S, Caslake MJ, et al. Acute suppression of VLDL1 secretion rate by insulin is associated with hepatic fat content and insulin resistance. Diabetologia. 2007;50:2356-65.

54. Guerrero-Romero F, Simental-Mendia LE, Gonzalez-Ortiz M, Martinez-Abundis E, Ramos-Zavala MG, Hernandez-Gonzalez SO, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab. 2010;95:3347-51.

55. Simental-Mendia LE, Simental-Mendia E, Rodriguez-Hernandez H, Rodriguez-Moran M, Guerrero-Romero F. The product of triglycerides and glucose as biomarker for screening simple steatosis and NASH in asymptomatic women. Ann Hepatol. 2016;15:715-20.

56. Nasr P, Fredrikson M, Ekstedt M, Kechagias S. The amount of liver fat predicts
mortality and development of type 2 diabetes in non-alcoholic fatty liver disease.
Liver Int 2020 Feb 22. doi: (in press).

57. Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a metaanalysis. Hepatology. 2011;54:1082–90.

Abbreviations
FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GGT, γ-glutamyltransferase; WC, waist circumference; WHR, waist-to-hip ration; WHtR, waist-to-height ratio; FLI, fatty liver index; TyG, triglyceride glucose index; T2DM, type 2 diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue

Figures
Figure 1

Receiver operating characteristic (ROC) curves of fatty liver index and triglyceride glucose index used to predict the presence of hepatic steatosis in overall women.
Figure 2

Receiver operating characteristic (ROC) curves of fatty liver index and triglyceride glucose index used to predict the presence of hepatic steatosis in women younger than 60 years.
Figure 3

Receiver operating characteristic (ROC) curves of fatty liver index and triglyceride glucose index used to predict the presence of hepatic steatosis in women over the age of 60 years.
Figure 4

Receiver operating characteristic (ROC) curves of fatty liver index, triglyceride glucose index (TyG) as well as the combination of TyG with obesity indices used to predict the presence of hepatic steatosis in overall women

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

Supplemental Table.docx
Supplemental Figure.docx