**Name of journal:** **World Journal of** **Gastroenterology**

**ESPS Manuscript NO: 22549**

**Manuscript Type: ORIGINAL ARTICLE**

***Observational Study***

**Fatty liver index value *vs* waist circumference for predicting of non-alcoholic fatty liver disease**

Motamed N *et al.* Predictive of NAFLD by FLI

Nima Motamed, Masoudreza Sohrabi, Hossein Ajdarkosh, Gholamreza Hemmasi, Mansooreh Maadi, Reza Pirzad, Khadijeh Abedi, Sivil Aghapour, Farhad Zamani

**Nima Motamed**, Department of social medicine, Zanjan University of Medical Sciences, Zanjan 45154, Iran

**Nima Motamed**, GastroIntestinal and Liver Disease Research Center, Iran University of Medical Sciences,Tehran 159347, Iran

**Nima Motamed**, **Masoudreza Sohrabi**, **Hossein Ajdarkosh**, **Gholamreza Hemmasi** , **Mansooreh Maadi**, **Reza Pirzad**, **Khadijeh Abedi**, **Sivil Aghapour, Farhad Zamani**, GastroIntestinal and Liver Disease Research Center, Iran University of Medical Sciences,Tehran 159347, Iran

**Fatemeh Sima Saeedian**, Department of Endocrinology, Sari University of Medical Sciences, Tehran 159347, Iran

**Mojtaba Fallahnezhad**, Razi Science Researchers Institute, Karaj 31976, Iran

**Author contributions:** Motamed N Study concept and design; analysis and interpretation of data; drafting of the manuscript; Sohrabi M data aquisation, Drafting of the manuscript; revision of the manuscript; Ajdarkosh H, Hemmasi G, Sayeedian FS Critical revision of the manuscript for important intellectual content; Maadi M acquisition of data; Administrative, technical, or material support; Fallahnezhad M and Aghapour S Administrative, technical, or material support; Zamani F Critical revision of the manuscript; study supervision manuscript; study supervision.

**Supported by** This project supported by GILDRC, Iran University of Medical Sciences.

**Institutional review board statement:** This study was reviewed and approved by the GastroIntestinal and liver Disease Research Center Review Board.

**Informed consent statement:** All involved persons, or their legal guardian, gave their informed consent prior to study.

**Conflict-of-interest statement:** There is no conflict of interest

**Data sharing statement:** Could be addressed to Farhad Zamani /Nima Motamed

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to: Farhad Zamani, MD, Professor,** Gastrointestinal and Liver Disease Research Center, Iran University of Medical Sciences, Firoozgar Hospital, BehAfarin Ave. Valiasr Sq, Tehran 159374, Iran. [zamani.f@iums.ac.ir](mailto:zamani.f@iums.ac.ir)

**Telephone:** +98-21-88940489

**Fax**: +98-21-88940489

**Received:** September 20, 2015

**Peer-review started:** September 21, 2015

**First decision:** October 14, 2015

**Revised:** November 5, 2015

**Accepted:** December 8, 2015

**Article in press:**

**Published online:**

**Abstract**

**AIM**: To determine the discriminatory performance of fatty liver index (FLI) for nonalcoholic fatty liver disease (NAFLD).

**METHODS**: The data of 5052 subjects aged over 18 years were analyzed. FLI was calculated based on data of body mass index, waist circumference (WC), triglyceride and gamma glutamyl transferase. Logistic regression analysis was conducted to determine the association between FLI and NAFLD. The discriminatory performance of FLI in the diagnosis of NAFLD was evaluated by receiver operating characteristic analysis. Area under the curves (AUCs) and related confidence intervals were estimated. Optimal cutoff points of FLI in the diagnosis of NAFLD were determined based on the maximum values of youden index.

**RESULTS:** The mean age of men and women were 44.8 ± 16.8 and 43.78 ± 15.43, respectively (*P* = 0.0216). The prevalence of NAFLD was 40.1 % in men and 44.2% in women (*P* < 0.0017). FLI was strongly associated with NAFLD, so that one unit increase in FLI increased the chance of developing NAFLD 5.8% (OR = 1.058, 95%CI: 1.054-1.063, *P* < 0.0001). Although FLI revealed a good performance in the diagnosis of NAFLD (AUC = 0.8656 (95%CI: 0.8548-0.8764), its performance had not significant difference with WC (AUC = 0.8533, 95%CI: 0.8419-0.8646). According sex the performance of FLI was not different between men(AUC = 0.8648, 95%CI: 0.8505-0.8791) and women (AUC = 0.8682, 95%CI: 0.8513-0.8851) while based on age the highest performance was related to the age group of 18-39 (AUC = 0.8930, 95%CI: 0.8766- 0.9093). The optimal cutoff points of FLI were 46.9 in men (sensitivity = 0.8242, specificity = 0.7687, Youden index = 0.5929) and 53.8 in women (sensitivity = 0.8233, specificity = 0.7655, Youden index = 0.5888).

**CONCLUSION:** FLI had an acceptable discriminatory power in the diagnosis of NAFLD, however WC as a more simple and accessible index revealed similar performance.

**Key words**: Non-alcoholic fatty liver disease; Fatty liver index; Discriminatory performance; Waist circumference; Body mass index; Optimal cutoff points

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The present study was carried out to evaluate the discriminatory capability of fatty liver index in the diagnosis of nonalcoholic fatty liver disease (NAFLD) among the general population of northern Iran. Our results showed that the chance of occurrence of NAFLD was increased by 5.8% due to one unit increase in fatty liver index (FLI). Although, we found the FLI has a good discriminatory power, its capability was not better than waist circumference (WC).

Motamed N, Sohrabi M, Ajdarkosh H, Hemmasi G, Maadi M, Pirzad R, Abedi K, Aghapour S, Zamani F. *World J Gastroenterol* 2015; In press

**INTRODUCTION**

Nonalcoholic fatty liver disease (NAFLD) is a chronic condition characterized by the accumulation of fat in the liver in the absence of other causes of steatosis, including excess consumption of alcohol or drugs[1]. The prevalence of this condition varied from 20% to 30% in western countries depending on applied diagnostic tools, the population under study and related definitions[2]. Although the prevalence in Asian countries is lower than western countries, an increasing trend has occurred in Asian countries due to the rise of incidence of obesity, metabolic syndrome and diabetes type 2 recently[3]. The prevalence of NAFLD is estimated 15%-20% in Asian population, however the prevalence was near to 44% in adults in northern Iran based on one population based study[3,4]. On the other hand, this disease can lead to a wide range of clinical conditions from simple steatosis to cirrhosis or even hepatocellular carcinoma[5-9].

Two most common methods used in the diagnosis of fatty liver are histologic methods and imaging procedures, however, no one diagnostic procedure has been shown to be reliable enough in the diagnosis of fatty liver[10-12]. Although liver biopsy is the gold standard procedure for diagnosis of NAFLD, this procedure is an invasive and expensive tool that has some health risks and economic costs[11-14].

Recently, a number of indices were introduced to diagnose NAFLD consisting of simple measures[15-18]. Fatty liver index (FLI) is one of these indices developed as a convenient tool based on body mass index (BMI), waist circumference (WC), triglyceride (TG) and gamma glutamyl transferase (GGT) levels[18]. In one previous study, this index showed a good predictive performance in the diagnosis of NAFLD, with an AUC of 0.813[19]. When a diagnostic tool displays accurate predictive capability, determination of an optimal cutoff point, for it will be highly interested. To the best knowledge of the authors, no such study has been conducted among the Iranian population. Therefore, this study was carried out to assess the discriminatory ability of FLI in the diagnosis of NAFLD among a population in northern Iran and, in addition, to propose an optimal cutoff point for FLI.

**MATERIALS AND METHODS**

***Study participants***

Of 6140 participants of a baseline cohort study conducted among individuals of 10 to 90 years of age, data of 5052 participants of 18 years of age and older were analyzed in the present study. The baseline study was carried out in Amol, a densely populated city in northern Iran. Local health centers were used to collect the data, where almost all study participants had health record files. Sampling of cohort study was explained elsewhere[20]. A schematic diagram of the study participants and exclusions was displayed in Figure 1.

***Data collection***

Weight, height, waist circumference, hip circumference and blood pressure were measured in health centers where trained healthcare staff members were responsible for data collection. Height was measured while the participants were standing with their heels and buttocks pressed up against a wall. Waist circumference was determined at the midpoint between the lowest costal ridge and the upper border of the iliac crest. The largest circumference between waist and knee was determined as hip circumference. The measurement was done with a non-stretchable and an accurately calibrated scale with 0.5 cm precision.

Blood pressure was measured, after a minimum 5-minute rest in a quiet room, with the use of a fitted cuff as participants were in the sitting position, their back supported and legs uncrossed. The systolic and diastolic blood pressures were determined and recorded as the first appearance and disappearance of Korotkof sounds, respectively.

A venous blood sample was drawn from each participant following 12-hour fasting to assess fasting blood sugar (FBS) and lipid profiles. All tests, including FBS, triglycerides (TGs), high-density lipoprotein (HDL), low-density lipoprotein and cholesterol were assessed enzymatically using the BS200 Auto analyzer (Mindray, China). For all of them viral markers for hepatitis B and C along with autoimmune hepatitis screening test were performed.

Ten percent of the blood samples were evaluated by the Iranian National Reference Laboratory with the coefficients of variation being between 1.7 and 3.8% of all laboratory values.

Nonalcoholic fatty liver disease (NAFLD) was determined by evidence of hepatic steatosis in the sonogram and no existence of other causes of acute or chronic hepatitis as well as secondary hepatic fat accumulation such as signiﬁcant *alcohol consumption*, use of *steatogenic medication* or *hereditary disorders*.

All ultrasound examinations were carried out by a single sonographer who was an expert in the field of radiology. A 3-5 MHz transducer was used to examine the liver parenchyma by which the sagittal, longitudinal, lateral and intercostal views of parenchyma were obtained. Steatosis was confirmed if a marked increase of hepatic echogenicity was diagnosed as well as if the hepatic vessels and diaphragm appeared abnormal.

Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated based on following formula: 

The FLI was calculated based on laboratory and anthropometric measures, including TG, GGT, BMI and WC by using the following formula:

***Statistical analysis***

The capability of FLI to discriminate between subjects with NAFLD and subjects without this condition was evaluated using receiver operating characteristic (ROC) curve for which the sensitivity of infinite decision thresholds of FLI was plotted against their false positive rates. Thus the related area under the curves (AUCs) were calculated. The lower boundary line for AUC was considered 0.5 which a significantly greater area than 0.5 shows some ability of FLI to discriminate patients with NAFLD from patients without it. The optimal cutoff point of FLI was also determined using maximal values of Youden’s J statistics (). The value of FLI corresponding to a maximum value of the Youden index was considered the optimal cutoff point for FLI.

Multivariable logistic regression analysis was conducted on NAFLD, as an outcome variable, and also relevant predictor variables. Five potential predictor variables, including age, gender, MAP, HDL, and the HOMA-IR test was entered into the model in addition to FLI. In the multivariable model, Cox and Snell’s and also Nagelkerke’s were calculated to determine how much variance of NAFLD could be explained by the model. The Hosmer and Lemeshow test was used to evaluate the adequacy or suitability of the model. The odds ratio and related confidence intervals along with p-values were reported. The significance level for all analyses was considered 0.05. All statistical analyses were conducted using version 21 of SPSS Inc, Chicago statistical software and STATA software, version 12 (StataCorp, Texas, United States).

**RESULTS**

Table 1 shows the mean age, anthropometric characteristics and laboratory values of the study participants. Significant differences were reported between the two sexes for all variables except TG.

***Results of ROC curve analysis***

In total population the AUC of FLI in the diagnosis of NAFLD was 0.8656 (95%CI: 0.8548-0.8764) in which no significant difference was detected between men (AUC = 0.8648, 95%CI: 0.8504-0.8791) and women (AUC = 0.8682, 95%CI: 0.8513-0.8851). The analysis according to age group showed the greatest capability was related to the age group of 18-40 (AUC=0.8930, 95%CI: 0.8766-0.9093) and the lowest accuracy was related to the age group of 40-60 (AUC = 0.8293, 95%CI: 0.8095-0.8492]). The AUC for the age group of ≥ 60 was 0.8403 (95%CI: 0.8124- 0.8683). Although the predictive performance of FLI was significantly higher than BMI (AUC of BMI = 0.8258, 95%CI: 0.8139- 0.8378), TG (AUC of TG = 0.6840, 95%CI: 0.6676-0.7004), and gamma glutamyl transferase (GGT) (AUC of GGT = 0.6927, 95%CI: 0.6772 - 0.7081) with *P* < 0.0001, no significant difference was detected between the performance of FLI and WC (AUC of WC = 0.8533, 95%CI: 0.8419-0.8646). Figure 2 shows the related ROC curves for FLI, WC, BMI, TG and GGT in men and women.

A gender-based optimal cutoff points of FLI were also obtained for FLI in the diagnosis of NAFLD. The optimal cutoff points of FLI were 46.9 in men (sensitivity = 0.8242, specificity = 0.7687, Youden index = 0.5929) and 53.8 in women (sensitivity = 0.8233, specificity = 0.7655, Youden index = 0.5888).

The prevalence of a high FLI, according to these cutoff points was 0.4809 (0.4610-0.5007) in men and 0.5021 (0.4782-0.5260) in women. No significant difference was detected between two sexes.

***Results of univariate and multivariate logistic regression analysis***

First univariate logistic regression analysis was performed on NAFLD entering predictor variables, including age, sex, systolic blood pressure, diastolic blood pressure, HOMA-IR test, HDL and FLI. The results of univariate logistic regression were reported in Table 2.

Before conducting multivariate model the suitability and adequacy of model was evaluated using relevant specific tests. In the multi- collinearity diagnostic test, SBP and DBP were located in a single common dimension and also a variance proportion of 0.97 was related to SBP. As a result, we replaced SBP and DBP with mean arterial pressure (MAP)[ in multivariate model. The collinearity tests were rechecked before conducting multivariable logistic regression of which no variance proportion ≥ 0.9 was related to predictor variables; tolerances varied from 0.599 to 0.951 and also each of the predictor variables was located separately in a related independent dimension. In multivariate model, Cox and Snell’s and Nagelkerke’s respectively denoted about 38.3% and 51.5% of the variance of NAFLD can be explained by the model. On the other hand, Hosmer and Lemeshow Test (chi-square = 14.476, df = 8 and *P* = 0.07) indicated a significant difference cannot be established between observed and expected frequencies and therefore the adequacy and suitability of our proposed model was confirmed. Removing the effects of other predictors in the multivariable model, age (*P* < 0.001), gender (*P* = 0.002), MAP (*P* = 0.002) and FLI (*P* < 0.001) were significantly associated with NAFLD. FLI was highly associated with NAFLD so that a one-unit increase in FLI increased the chance of occurrence of NAFLD by 5.8%. The odds ratios of the other predictor variables are shown in Table 2.

Table 3 shows the prevalence of NAFLD and a high FLI, where the latter was calculated based on our study cutoff points. The second and third columns of this table are related to the prevalence of NAFLD and a high FLI. Although among women an increasing trend of prevalence of NAFLD was detected according to age, among men the prevalence was highest in the age group of 40-59. We observed a similar pattern for a high FLI.

**DISCUSSION**

The present study revealed that FLI has a high discriminatory power in the diagnosis of NAFLD. Analyses based on sex and age groups showed that this index has an appropriate performance in both sex and all age groups of 18-39, 40-59 and ≥ 60. A significantly strong association between NAFLD and FLI was also confirmed by binary regression so that a one-unit increase in FLI led to a 5.8% increase in the chance of developing NAFLD. These results were in line with the findings of a previous study in which FLI showed a good predictive performance in the diagnosis of NAFLD, with an AUC of 0.813[19].

This result could be somewhat anticipated due to the fact that FLI is composed of four quantities related to NAFLD including BMI, WC, GGT and TG[18]. A high BMI or WC, as main obesity indices, is considered an essential risk factor for NAFLD and the prevalence of NAFLD substantially increases in obese individuals[21]. GGT can be considered an independent predictor for NAFLD since this enzyme increases in NAFLD to protect against the adverse effects of insulin resistance due to its antioxidant activity[22,23]. On the other hand, among the markers of dyslipidemia, TG is strongly associated with NAFLD[24]. However, we found no significant difference between the performance of FLI and WC. An almost equal performance between obesity indices and FLI could be somewhat expected, because not only obesity is strongly associated with NAFLD, but it is also associated with other components involved in the calculation of FLI including TG and liver enzymes[25,26]. On the other hand, insulin resistance plays a key role in the pathogenesis of NAFLD and there is also a strong association between this condition and the abnormal components of metabolic syndrome (MetS), where the NAFLD is considered the hepatic manifestation of MetS[27]. As a result, a high discriminatory capability of WC for NAFLD is a logical expectation due to an undeniable role of visceral adiposity in MetS. However Koehler et al obtained a slightly but significantly higher performance for FLI than obesity indices in elderly inhabitants of a district of Rotterdam, The Netherlands[19].

This study also suggests separate optimal cutoff points of FLI for men and women with values of 46.9 and 53.8, respectively. A higher cutoff point for women is perhaps the result of a lower vulnerability of females to this condition due to the protective effect of estrogen, although its underlying mechanism is not fully known[28,29]. Furthermore, metabolic risk factors alone play different roles in the development of NAFLD between males and females[30].

Although NAFLD has previously been discussed as a predominantly male condition, our study obtained a significantly higher prevalence of it among women compared to men[31]. This disagreement may be partly attributed to the markedly higher prevalence of obesity among women (47.3%) compared to men (21.6%). On the other hand, despite a higher estimation of NAFLD among women, our results appear to confirm that the female sex has a protective mechanism against NAFLD. In univariable analysis the women seemed to show greater odds than men for developing NAFLD, but by removing the effects of other predictors in the multivariable model, an inverse result was obtained, in such a way that a higher chance of NAFLD was then related to the male sex**.**  On the other hand, men had a higher prevalence of NAFLD in the under-40 age group than women, while prevalence was higher in women than men in the over-60 age group perhaps as a result of an attenuated protective effect of estrogen against NAFLD in menopause women. Moreover, the prevalence of fatty liver among men was reduced in the over-60 age group compared with the 40-60-year-old group which could be due to the declining effects of male sexual hormones[32].

Our study had a population based design and also a large sample size in which a reliable non-invasive approach was applied to diagnose NAFLD. Although liver biopsy is the gold standard for diagnosis of fatty liver disease, this approach not only is an invasive procedure, but also has a relatively high false negative rate in the diagnosis of this condition[10-12,33]. As a result, it may be better, a multifaceted non-invasive approach is implemented to diagnose NAFLD in population based studies until a more reliable evaluation can be obtained from the performance of FLI.

In conclusion, FLI has a promising predictive power in the diagnosis NAFLD. However, according to our findings, FLI was not more effective than WC in the discrimination of NAFLD. While the performance of FLI was not different between the two sexes, a higher cutoff point of FLI was obtained for women than men.

**ACKNOWLEDGEMENTS**

The authors would like to express their gratitude to Iran University Medical Sciences and Tehran University of Medical Sciences for their support of this project; to the staff and management of Hefdah Shahrivar Hospital, in Amol, Iran, for their cooperation; to the members of the Amol Cohort Study Center.

**COMMENTS**

***Background***

Nonalcoholic fatty liver disease (NAFLD) is a chronic condition. The prevalence of this condition varied from 20% to 30% in different countries. The most common methods used in the diagnosis of fatty liver are histological and imaging procedures that have own limitations. Never the less, this disease can lead to a wide range of clinical conditions and as a result make its diagnosis difficult. In this context recently some indices were introduced to diagnose NAFLD, fatty liver index (FLI) is one of them that has a good prediction value in previous reports.

***Research frontiers***

It is estimated that the prevalence of NAFLD among Asian and Middle East population is more than 20%, however based on some cohort studies in Iran this rate reach to 40%. Therefore usage of a simple diagnostic modality with high predictive value for detection of NAFLD is an important issue in this region.

***Innovations and breakthroughs***

In Iran as other countries the prevalence of NAFLD has a increasing trend that is predicted that we face to major health problem in near future. Therefore, its early diagnosis of NAFLD become more important .In this study we revealed that FLI had a high discriminatory power in the diagnosis of NAFLD in our population. In addition, according the gender the performance of FLI was not different between two genders. Furthermore, the highest performance of FLI was seen in the age group of 18-39. The optimal cutoff points of FLI were 46.9 in men and 53.8 in women.

***Applications***

Based on present study we can suggest that WC almost has same value as FLI in practice. In fact, WC could consider as a easy and economic modality with high discrimination value for detection of NAFLD.

***Terminology***

NAFLD is a chronic condition with vast clinical presentation which is characterized by the accumulation of fat in the liver in the absence of other causes of steatosis, including excess consumption of alcohol or drugs*.* The FLI was calculated based on laboratory and anthropometric measures, including TG, GGT, BMI and WC by using a specific formula.

***Peer-review***

There is not enough data regarding diagnosis and discrimination of NAFLD particularly in Middle East region. This study present the discrimination power of FLI and its cut-of-point for NAFLD. The result are noticeable according to our findings, FLI has not superiority to WC in the discrimination of NAFLD. Furthermore, the performance of FLI was not different between the two sexes; but a higher cutoff point of FLI was obtained for women than men.

**REFERENCES**

1 **Angulo P**, Lindor KD. Non-alcoholic fatty liver disease. *J Gastroenterol Hepatol* 2002; **17** Suppl: S186-S190 [PMID: 12000605]

2 **Neuschwander-Tetri BA**, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology* 2003; **37**: 1202-1219 [PMID: 12717402]

3 **Ashtari S**, Pourhoseingholi MA, Zali MR. Non-alcohol fatty liver disease in Asia: Prevention and planning. *World J Hepatol* 2015; **7**: 1788-1796 [PMID: 26167252 DOI: 10.4254/wjh.v7.i13.1788]

4 **Amirkalali B**, Poustchi H, Keyvani H, Khansari MR, Ajdarkosh H, Maadi M, Sohrabi MR, Zamani F. Prevalence of Non-Alcoholic Fatty Liver Disease and Its Predictors in North of Iran. *Iran J Public Health* 2014; **43**: 1275-1283 [PMID: 26175982]

5 **Vernon G**, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011; **34**: 274-285 [PMID: 21623852 DOI: 10.1111/j.1365-2036.2011.04724.x]

6 **Matteoni CA**, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999; **116**: 1413-1419 [PMID: 10348825]

7 **Caldwell SH**, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology* 1999; **29**: 664-669 [PMID: 10051466]

8 **Clark JM**, Diehl AM. Nonalcoholic fatty liver disease: an underrecognized cause of cryptogenic cirrhosis. *JAMA* 2003; **289**: 3000-3004 [PMID: 12799409]

9 **Harrison SA**, Torgerson S, Hayashi PH. The natural history of nonalcoholic fatty liver disease: a clinical histopathological study. *Am J Gastroenterol* 2003; **98**: 2042-2047 [PMID: 14499785]

10 **Otgonsuren M**, Estep MJ, Hossain N, Younossi E, Frost S, Henry L, Hunt S, Fang Y, Goodman Z, Younossi ZM. Single non-invasive model to diagnose non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). *J Gastroenterol Hepatol* 2014; **29**: 2006-2013 [PMID: 25039333 DOI: 10.1111/jgh.12665]

11 **Ratziu V**, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology* 2005; **128**: 1898-1906 [PMID: 15940625]

12 **Wieckowska A**, Feldstein AE. Diagnosis of nonalcoholic fatty liver disease: invasive versus noninvasive. *Semin Liver Dis* 2008; **28**: 386-395 [PMID: 18956295 DOI: 10.1055/s-0028-1091983]

13 **Chalasani N**, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 2012; **55**: 2005-2023 [PMID: 22488764 DOI: 10.1002/hep.25762]

14 **Conlon BA**, Beasley JM, Aebersold K, Jhangiani SS, Wylie-Rosett J. Nutritional management of insulin resistance in nonalcoholic fatty liver disease (NAFLD). *Nutrients* 2013; **5**: 4093-4114 [PMID: 24152749 DOI: 10.3390/nu5104093]

15 **Poynard T**, Ratziu V, Naveau S, Thabut D, Charlotte F, Messous D, Capron D, Abella A, Massard J, Ngo Y, Munteanu M, Mercadier A, Manns M, Albrecht J. The diagnostic value of biomarkers (SteatoTest) for the prediction of liver steatosis. *Comp Hepatol* 2005; **4**: 10 [PMID: 16375767]

16 **Poynard T**, Ratziu V, Charlotte F, Messous D, Munteanu M, Imbert-Bismut F, Massard J, Bonyhay L, Tahiri M, Thabut D, Cadranel JF, Le Bail B, de Ledinghen V. Diagnostic value of biochemical markers (NashTest) for the prediction of non alcoholo steato hepatitis in patients with non-alcoholic fatty liver disease. *BMC Gastroenterol* 2006; **6**: 34 [PMID: 17096854]

17 **Poynard T**, Imbert-Bismut F, Munteanu M, Ratziu V. FibroTest-FibroSURE: towards a universal biomarker of liver fibrosis? *Expert Rev Mol Diagn* 2005; **5**: 15-21 [PMID: 15723588]

18 **Bedogni G**, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, Tiribelli C. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol* 2006; **6**: 33 [PMID: 17081293]

19 **Koehler EM**, Schouten JN, Hansen BE, Hofman A, Stricker BH, Janssen HL. External validation of the fatty liver index for identifying nonalcoholic fatty liver disease in a population-based study. *Clin Gastroenterol Hepatol* 2013; **11**: 1201-1204 [PMID: 23353640 DOI: 10.1016/j.cgh.2012.12.031]

20 **Zamani F**, Sohrabi M, Alipour A, Motamed N, Saeedian FS, Pirzad R, Abedi K, Maadi M, Ajdarkosh H, Hemmasi G, Khonsari M. Prevalence and risk factors of cholelithiasis in Amol city, northern Iran: a population based study. *Arch Iran Med* 2014; **17**: 750-754 [PMID: 25365614 DOI: 0141711/AIM.006]

21 **Milić S**, Lulić D, Štimac D. Non-alcoholic fatty liver disease and obesity: biochemical, metabolic and clinical presentations. *World J Gastroenterol* 2014; **20**: 9330-9337 [PMID: 25071327 DOI: 10.3748/wjg.v20.i28.9330]

22 **Bi WR**, Yang CQ, Shi Q, Xu Y, Cao CP, Ling J, Wang XY. Large-scale analysis of factors influencing nonalcoholic fatty liver disease and its relationship with liver enzymes. *Genet Mol Res* 2014; **13**: 5880-5891 [PMID: 25117346 DOI: 10.4238/2014.August.7.3]

23 **Ma H**, Xu C, Xu L, Yu C, Miao M, Li Y. Independent association of HbA1c and nonalcoholic fatty liver disease in an elderly Chinese population. *BMC Gastroenterol* 2013; **13**: 3 [PMID: 23294935 DOI: 10.1186/1471-230X-13-3]

24 . Triglyceride is strongly associated with nonalcoholic fatty liver disease among markers of hyperlipidemia and diabetes. *Biomed Rep* 2014; **2**: 633-636 [PMID: 25054002]

25 **Lam GM**, Mobarhan S. Central obesity and elevated liver enzymes. *Nutr Rev* 2004; **62**: 394-399 [PMID: 15508909]

26 **Liu J**, Fox CS, Hickson DA, May WD, Hairston KG, Carr JJ, Taylor HA. Impact of abdominal visceral and subcutaneous adipose tissue on cardiometabolic risk factors: the Jackson Heart Study. *J Clin Endocrinol Metab* 2010; **95**: 5419-5426 [PMID: 20843952 DOI: 10.1210/jc.2010-1378]

27 **Tarantino G**, Finelli C. What about non-alcoholic fatty liver disease as a new criterion to define metabolic syndrome? *World J Gastroenterol* 2013; **19**: 3375-3384 [PMID: 23801829 DOI: 10.3748/wjg.v19.i22.3375]

28 **Gutierrez-Grobe Y**, Ponciano-Rodríguez G, Ramos MH, Uribe M, Méndez-Sánchez N. Prevalence of nonalcoholic fatty liver disease in premenopausal, posmenopausal and polycystic ovary syndrome women. The role of estrogens. *Ann Hepatol* 2010; **9**: 402-409 [PMID: 21057159]

29 **McKenzie J**, Fisher BM, Jaap AJ, Stanley A, Paterson K, Sattar N. Effects of HRT on liver enzyme levels in women with type 2 diabetes: a randomized placebo-controlled trial. *Clin Endocrinol* (Oxf) 2006; **65**: 40-44 [PMID: 16817817]

30 **North KE**, Graff M, Franceschini N, Reiner AP, Feitosa MF, Carr JJ, Gordon-Larsen P, Wojczynski MK, Borecki IB. Sex and race differences in the prevalence of fatty liver disease as measured by computed tomography liver attenuation in European American and African American participants of the NHLBI family heart study. *Eur J Gastroenterol Hepatol* 2012; **24**: 9-16 [PMID: 21900826]

31 **Browning JD**, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; **40**: 1387-1395 [PMID: 15565570]

32 **Zhang H**, Liu Y, Wang L, Li Z, Zhang H, Wu J, Rahman N, Guo Y, Li D, Li N, Huhtaniemi I, Tsang SY, Gao GF, Li X. Differential effects of estrogen/androgen on the prevention of nonalcoholic fatty liver disease in the male rat. *J Lipid Res* 2013; **54**: 345-357 [PMID: 23175777 DOI: 10.1194/jlr.M028969]

33 **Rockey DC**, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. *Hepatology* 2009; **49**: 1017-1044 [PMID: 19243014 DOI: 10.1002/hep.22742]

**P-Reviewer:** He JY, Tarantino G, Zhu X **S-Editor:** Qi Y **L-Editor: E-Editor:**

**Table 1** **Anthropometric characteristics and laboratory values of participants**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | | **Men (*n* = 2860)** | **Women (*n* = 2192)** | ***P* value** |
| Meam ± SD | |
| Age (yr) | | 44.77 ± 16.77 | 43.78 ± 15.43 | 0.0216 |
| Weight (kg) | | 76.70 ± 15.05 | 72.60 ± 14.36 | < 0.0001 |
| Height (cm) | | 169.94 ± 8.02 | 156.40 ± 7.05 | < 0.0001 |
| WC (cm) | | 90.76 ± 12.32 | 91.55 ± 13.89 | 0.0199 |
| DBP (mmHg) | | 76.61 ± 12.69 | 75.82 ± 13.05 | 0.0191 |
| SBP (mmHg) | | 117.42 ± 15.76 | 115.42 ± 17.60 | < 0.0001 |
| MAP (mmHg) | | 90.22 ± 12.90 | 89.01 ± 13.62 |  |
| BMI (/ | Mean ± SD | 26.46 ± 4.60 | 29.65 ± 5.67 | < 0.0001 |
| Prevalence of BMI ≥ 30 (%) | 21.6 (20.2- 23.0) | 47.3 (45.4-49.3) |
| TG (mg/dL) | | 145.55 ± 98.25 | 141.12 ± 95.99 | 0.0966 |
| HDL (mg/dL) | | 43.37 ± 11.48 | 46.42 ± 12.08 | < 0.0001 |
| Cholesterol | | 178.49 ± 41.95 | 189.47 ± 43.20 | < 0.0001 |
| ALT (U/L) | | 26.46 ± 19.04 | 19.59 ± 14.03 | < 0.0001 |
| AST (U/L) | | 23.98 ± 12.65 | 19.98 ± 9.71 | < 0.0001 |
| GGT (U/L) | | 29.90 ± 28.61 | 25.62 ± 21.64 | < 0.0001 |
| FBS | | 98.62 ± 29.86 | 103.98 ± 41.30 | < 0.0001 |
| Insulin(mU/L) | | 8.87 ± 6.74 | 10.36 ± 6.88 | < 0.0001 |
| HOMA-IR | | 2.19 ± 1.90 | 2.72 ± 2.45 | < 0.0001 |
| FLI | | 45.76 ± 28.93 | 52.24 ± 29.87 | < 0.0001 |

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BMI: Body Mass Index; DBP: Diastolic Blood Pressure; GGT: Gamma Glutamyl Transferase; FBS: Fasting Blood Sugar; FLI: Fatty liver index; HDL: High-density lipoprotein; HOMA-IR: Homeostasis Model Assessments-insulin resistance; LDL: Low-density lipoprotein; MAP: Mean Arterial Pressure; SBP: Systolic Blood pressure; SD: Standard Deviation; TG: Triglyceride; WC: Waist Circumference.

**Table 2 Results of univariable and multivariable logistic regression analysis, including Wald tests, related *P*-value and odd ratios**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **Univariable logistic regression** | | | **Multivariable logistic regression** | | |
| **Wald test** | ***P* value** | **Odds ratio and CI** | **Wald test** | ***P* value** | **Odds ratio** |
| Age | 408.6 | < 0.001 | 1.037 (1.033-1.040) | 56.7 | < 0.001 | 1.022 (1.016-1.028) |
| Gender | 9.828 | 0.002 | 1.183 (1.065-1.315) | 9.020 | 0.003 | 0.764 (0.641-0.911) |
| MAP | 476.4 | < 0.001 | 1.052 (1.047-1.057) | 9.225 | 0.002 | 1.011 (1.004-1.018) |
| HOMA-IR | 364.3 | < 0.001 | 1.408 (1.359-1.4457) | 2.402 | 0.121 | 1.036 (0.991-1.084) |
| HDL | 273.7 | 0.001 | 0.959 (0.954-0.964) | 1.381 | 0.240 | 1.005 (0.997-1.013) |
| FLI | 1148.9 | < 0.001 | 1.061 (1.058-1.065) | 722.5 | < 0.001 | 1.058 (1.054-1.063) |

CI: Confidence interval; FLI: Fatty liver index; HDL: High-density lipoprotein; HOMA-IR: Homeostasis Model Assessments- insulin resistance; MAP: Mean Arterial Pressure.

**Table 3** **Prevalence of nonalcoholic fatty liver disease and a high** **fatty liver index by sex and age groups**

|  |  |  |
| --- | --- | --- |
| **Population** | **Prevalence of NAFLD (%)** | **Prevalence of NAFLD High FLI1 (%)** |
| Men | | |
| Total men (*n* = 2860) | 40.1 (38.4-41.8) | 48.1 (46.1-50.1) |
| 18-39 (*n* = 1136) | 27.3 (24.9-29.7) | 37.6 (34.6- 40.7) |
| 40-59 (*n* =1124) | 50.6 (47.8-53.3) | 58.3 (55.2-61.5) |
| ≥60 (600) | 44.6 (40.9-48.3) | 48.9 (44.6-53.2) |
| Women | | |
| Total women(*n* =2192) | 44.2 (42.3-46.1) | 50.2 (47.8-52.6) |
| 18-39 (*n* = 902) | 20.4 (17.9-22.9) | 28.4 (24.9-31.8) |
| 40-59 (*n* = 900) | 59.4 (56.4-62.4) | 63.3 (59.7-66.9) |
| ≥ 60 (390) | 64.1 (59.6-68.5) | 66.4 (61.3-71.5) |

1Prevalence of a high FLI based on Cutoff points 46.9 for men and 53.8 for women. FLI: Fatty liver index; NAFLD: Nonalcoholic fatty liver disease.

808 subjects did not agree to participate in the study

7104 subjects aged 10-90 years were selected to participate in the cohort study

153 pregnant women were excluded

6296 subjects agree

346 subjects <18 were excluded

6143 subjects 10-90 years were included in the cohort study

486 subjects were excluded due to a history of excess alcohol consumption, a positive test of HBsAg and Anti HCV Ab and regularly consumption of drugs associated with fatty liver disease

5797 subjects of cohort study were ≥18 years

The data of 259 subjects were not appropriate to analyze for the present study

5311 subjects were included in the present study

Finally the data of 5052 subjects were analyzed

**Figure 1 Schematic diagram of the study participants and exclusions.**

****

Fig 2A



Fig 2B

**Figure 2 Receiver operating characteristic curves of fatty liver index and their related components.** A and B were related to men and women, respectively. Red color dash pattern curve was related to WC, yellow color solid pattern curve was related to BMI, blue color dot pattern curve was related to GGT, purple color long dash\_3dot pattern curve was related to TG and lime color dash dot pattern curve was related to FLI. BMI: Body mass index; FLI: Fatty liver index; GGT: Gamma glutamyl transferase; TG: Triglyceride; WC: Waist circumference.