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Biomarkers in Medicine

Assessing the clinical utility of major indices for nonalcoholic fatty liver disease in East Asian populations

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Nonalcoholic fatty liver disease (NAFLD) is currently the most common form of chronic liver disease. The growing prevalence of NAFLD is strongly associated with the high incidence of metabolic syndrome. NAFLD affects as much as 19% of the US population with a disproportionate impact on minority racial groups such as Asian Americans. If not promptly managed, NAFLD may progress to more feared complications. Liver indices for NAFLD screening have been proposed but were often developed using study populations with different anthropometrics than patients of East Asian descent. This review compares the accuracy of five indices for NAFLD screening in Asian cohorts. The Fatty Liver Index performed well in multiple large-scale community studies, although other indices may be more suited for specific patient cohorts. This is important, as the utilization of liver indices could accelerate screening for NAFLD for early management and to reduce liver disease-related health disparities among Asian Americans.

First draft submitted: 18 March 2023; Accepted for publication: 16 June 2023; Published online: 14 July 2023

Keywords: Asian subgroups • diagnostics • Fatty Liver Index • hepatology • nonalcoholic fatty liver disease • predictive index • steatosis • validation study

Background

Nonalcoholic fatty liver disease (NAFLD) is currently the most common form of chronic liver disease, affecting as many as 1 billion people worldwide [1]. In the USA, the estimated population prevalence of NAFLD was estimated to be 18.8%, with an annual medical cost of US $292 billion [1,2]. NAFLD encompasses a wide spectrum of pathological changes in the liver and is defined by hepatic fatty deposition without secondary causes such as excessive alcohol consumption [3]. Mild manifestations of NAFLD include isolated steatosis that can progress to steatohepatitis, fibrosis, cirrhosis and eventually hepatocellular carcinoma [4]. End-stage liver diseases such as NAFLD-related cirrhosis and hepatocellular carcinoma carry poor survival for patients and are the leading indications for liver transplant [4].

Known risk factors associated with adult NAFLD are similar to those of metabolic syndromes, including obesity, hypertension, Type 2 diabetes and dyslipidemia [3]. Certain comorbidities such as gout and hyperuricemia are shown to increase the risk even further [5]. Immigration and acculturation among to the Western world among Asian immigrants have been also shown to increase their risk of metabolic syndrome and cardiovascular diseases, escalating their propensity to develop NAFLD [6]. Given that many of these comorbidities disproportionately affect persons of East Asian descent, they may contribute to a greater risk of NAFLD in the Asian population [5,7,8]. The pathophysiology behind NAFLD is likely multifactorial, and studies have suggested that the initial fat accumulation is due to liver intake of excess circulating free fatty acids as a result of insulin insensitivity [9]. Steatosis in turn creates an environment that augments oxidative stress, contributing to the ballooning, inflammation and cell death of liver cells [9]. Dysregulation of the gut microbiome, as well as genetic predispositions, are also thought to contribute to the overall pathogenesis [9].

Of importance, NAFLD can also develop at a young age, occurring in as many as 70–80% of overweight and obese children [10]. Studies have shown that, in children with NAFLD, about 25–50% have steatohepatitis and 20–25% have advanced liver fibrosis at initial presentation [11]. This is alarming in that NAFLD in the pediatric population often progresses to an irreversible stage with limited interventions available once detected. This is associated with greater hepatic and extrahepatic morbidity. Because of the mortality rates associated with NAFLD and its sequelae, in addition to the significant economic implications, overall early detection of NAFLD is therefore necessary for timely management to prevent its progression to a more severe stage.

Liver biopsy is currently the established gold standard for the diagnosis of NAFLD [9]. The procedure is invasive in nature and associated with postoperative complications varying from pain to sepsis in about 1–3% of patients [9]. For this reason, imaging modalities are preferred as a first-line approach to diagnosing NAFLD. Abdominal ultrasound is widely employed for visualizing the liver structure. Though accessible, it has low sensitivity in patients with mild steatosis of less than 30% [1]. Computed tomography (CT) is also employed but is limited by radiation exposure and low sensitivity in select patient populations. Magnetic resonance spectroscopy provides the best resolution, but its high cost makes it less accessible [9].

In asymptomatic individuals, screening for NAFLD with the previously discussed diagnostic approaches may not be cost-effective [12]. This drives the need for an alternative, noninvasive method to accurately predict the presence of hepatic steatosis. Clinicians and scientists have devised different algorithms over the years, with the Fatty Liver Index (FLI) being the most validated and endorsed by multiple guidelines, including the European Association for the Study of the Liver [13]. Since the original study was validated in Italian patients, it is uncertain if the index has the same utility in predicting NAFLD in other demographics, such as in an Asian population. Research has shown that Asian Americans with NAFLD may present atypically with earlier onset, normal ALT level, as well as lower BMI and waist circumference, which are some commonly used variables in these predictive liver indices [14,15]. Although there is inconsistent data on the prevalence of NAFLD in Asian Americans, some studies report an estimate as high as 40%. This poses a significant public health risk to this population group. Furthermore, some subsets of Asian Americans incur a greater risk of comorbidities such as hypertension, dyslipidemia and diabetes [7], which are known risk factors for developing NAFLD. This disproportionate impact of metabolic syndromes in Asian Americans likely contributes to excess risk for NAFLD beyond the traditional risk factors and requires timely detection and intervention to prevent NAFLD progression to more severe complications.

Objectives

The goal of this work was to assess the validity and reliability of major liver indices in predicting NAFLD in East Asian patients and their role as early screening tools to identify individuals requiring further workup with diagnostic tools. This is of particular interest in the USA, as the Asian diaspora is one of the fastest-growing minority groups and has a greater prevalence of metabolic syndromes compared with non-Hispanic whites [16,17]. This constitutes a major risk factor for developing fatty liver disease and calls for an accessible and quick screening tool to be utilized. However, there is a gap in knowledge in the performance of various liver indices among Asian subgroups and this comprehensive review aims to summarize and synthesize up-to-date evidence for a patient-centered approach to detecting NAFLD.

Methods

To identify commonly utilized liver indices, the search terms 'liver index', 'predictive value' and 'fatty liver disease' were used in the initial screening of articles on PubMed. Five indices that were externally validated in at least two studies with Asian populations were chosen. Each index was further searched in association with the keywords 'Asian', 'validation study' and 'prognostic value' in various combinations. The inclusion criteria were primary research articles in the English language only. The search excluded results pertaining to the non-East Asian population to limit the scope of discussion and studies that focused solely on alcohol-related liver diseases.

Results

The research method identified five major NAFLD indices, including the FLI, Fatty Liver Disease Index (FLDI), Hepatic Steatosis Index (HSI), Zhenjiang University (ZJU) Index and Framingham Steatosis Index (FSI). A summary of these NAFLD indices is shown in Table 1. A majority of the studies were retrospective and utilized patient populations who received care at an affiliated hospital. Only one study examined NAFLD among the pediatric population. Cohorts with certain medical conditions such as obstructive sleep apnea and hepatitis B (hep

Table 1. Original studies used in generating fatty liver disease indices.

Index (year)	Variables/index formula	Patient characteristics	Primary results	Comments	Ref.
FLI (2006)	BMI, waist circumference, triglycerides and GGT FLI = $(e^{0.953\times \log e(\text{triglycerides})+0.139\times \text{BMI}+0.718\times \log e(\text{GGT})+0.053\times \text{waistcircumference}-15.745})/(1+e^{0.953\times \log e(\text{triglycerides})+0.139\times \text{BMI}+0.718\times \log e(\text{GGT})+0.053\times \text{waistcircumference}-15.745})\times 100$	224 residents with suspected liver disease (mean age = 58) and 287 without (mean age = 57) from Campogalliano	FLI had an accuracy of 0.84 Score <30 rules out NAFLD with a negative likelihood ratio of 0.2 and score >60 rules in NAFLD with a positive likelihood ratio of 4.3	Derived from ultrasound, did not use gold-standard liver biopsy Cannot classify severity of NAFLD Decreased accuracy when applied to obese patients	[13,18]
HSI (2010)	BMI, ALT/AST ratio, sex and diabetes mellitus status HSI = 8 × (ALT/AST ratio) + BMI (+2 if diabetes mellitus; +2 if female)	5362 patients with NAFLD and 5362 matched controls with a mean age of 52.2 from Seoul National University Hospital	AUROC in validation group was 0.819 Score <30 rules out NAFLD with sensitivity of 93.9% and score >36 rules in NAFLD with specificity of 93.1%	Derived from ultrasound, did not use gold-standard liver biopsy Significant correlation with degree of fatty liver Detected fatty liver diseases in pediatrics group with high accuracy	[12]
FLDI (2013)	BMI, triglycerides, ALT/AST ratio and hyperglycemia FLD index = BMI + triglycerides + 3 × (ALT/AST ratio) + 2 × HG (presence of hyperglycemia = 1, absence of hyperglycemia = 0)	3463 patients with NAFLD and 3463 matched controls with a mean age of 43.9 from Rizhao People's Hospital	AUROC was 0.817 in validation set Score <28 excludes NAFLD with sensitivity of 94.9% while >37 detects NAFLD with specificity of 96%	Derived from ultrasound, did not use gold standard liver biopsy Cannot classify the severity of NAFLD Not validated in non-Chinese populations	[19]
ZJU Index (2015)	BMI, triglycerides, ALT/AST ratio and fasting glucose level ZJU index = BMI + fasting blood glucose + triglycerides + 3× ALT/AST (+2 if female)	4801 NAFLD patients and 4801 matched controls with a mean age of 47.97 from the First Affiliated Hospital Zhejiang University	AUROC was 0.826 in validation cohort Score <32 rules out NAFLD with sensitivity of 92.4% and score >38 rules in NAFLD with specificity of 93.3%	Derived from ultrasound but was validated in a small sample of patients with liver biopsy High predictive values for younger patients (<40)	[20]
FSI (2016)	Age, sex, BMI, triglycerides, hypertension, diabetes and ALT/AST ratio FSI = −7.981 + 0.011 × age (years) − 0.146 × sex (female = 1, male = 0) + 0.173 × BMI (kg/m^2) + 0.007 × triglycerides (mg/dl) + 0.593 × hypertension (yes = 1, no = 0) + 0.789 × diabetes (yes = 1, no = 0) + 1.1 × ALT/AST ratio ≥1.33 (yes = 1, no = 0)	1181 participants with a mean age of 50 from Framingham Heart Study third-generation cohort and 4489 adults from National Health Nutrition Examination Survey III	C-statistic = 0.760 in validation cohort At a score of 23, sensitivity is 79% and specificity is 71%	Derived from CT, did not use gold-standard liver biopsy Index was validated in multiethnic cohort Initial derivation does not account for those with viral hepatitis	[21]

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AUROC: Area under receiver operating curve; CT: Computed tomography; FLDI: Fatty Liver Disease Index; FLI: Fatty Liver Index; FSI: Framingham Steatosis Index; GGT: Gamma-glutamyl transferase; HG: Hyperglycemia; HSI: Hepatic Steatosis Index; NAFLD: Nonalcoholic fatty liver disease; ZJU: Zhejiang University Index.

B) were included for the validation of NAFLD indices. Evaluation of the accuracy and utility of these liver indices in identifying fatty liver diseases in East Asians is described next.

Fatty Liver Index

The FLI was devised in 2006 by a group of researchers in Italy and is currently the most-validated tool for predicting fatty liver diseases [13]. It is recommended or endorsed by several professional organizations, including the European Association for the Study of the Liver and the Asian Pacific Association for the Study of the Liver. Comprised of four variables, BMI, waist circumference, triglyceride levels and gamma-glutamyl transpeptidase, the FLI in the original study showed an accuracy of 0.84 in detecting fatty liver disease compared with ultrasonography diagnosis [18]. Using scores derived from the index formula, the study determined a cutoff of <30 for ruling out and >60 for ruling in NAFLD with a sensitivity of 61% and specificity of 86%. The FLI was externally validated in a population-based study in the Netherlands, with an area under the receiver operating curve (AUROC) of 0.813 using the same threshold of <30 and >60 for exclusion and inclusion of NAFLD, respectively [22].

Due to the FLI's success in screening large population sizes in a noninvasive manner, researchers in Asia investigated whether it would have the same accuracy in detecting fatty liver diseases locally. When using the pre-established cutoff scores, the AUROC for detecting fatty liver disease was only 0.68 in one retrospective analysis involving 1301 Korean patients [23]. This was partly attributed to using MRI as the diagnostic tool, which has higher detection of mild hepatic steatosis and lower operator/observer error compared with ultrasonography. Another study in which 4009 Korean patients underwent routine health checkups similarly produced an unfavorable AUROC of

0.63 using the original cutoffs [24]. This improved, however, when the cutoff for diagnosis was modified to >31 and >18 in male and female patients, respectively. This highlights the importance of adjusting the cutoff threshold for the FLI to maximize its accuracy in detecting NAFLD, as target population characteristics can vary from those of the original study group [18].

Using an adjusted threshold, the accuracy of the FLI in detecting NALFD improved in select population demographics. In one large study involving 8626 middle-aged and elderly Chinese patients in the Jiading District of Shanghai, the AUROC for the FLI compared with ultrasonography in the overall population was 0.834 [25]. This can be further stratified by sex, with slightly better FLI performance in females (0.841) than in males (0.834). The authors adjusted the cutoffs for diagnosis to >30, which achieved the highest Youden's J Index of 0.51 with a specificity of 71.51% and sensitivity of 79.89%. A similar study was conducted in Taiwan, where 29,797 patients with an average age of 52.2 were enrolled to validate the accuracy of the FLI in identifying fatty liver disease diagnosed by ultrasound [26]. The group found that the AUROC for the overall population was 0.827. In addition, the optimal cutoffs for exclusion and inclusion were <25 and >35 for men, respectively, and <10 and >20 for women, respectively. Both thresholds were lower than the established level in the original study [18].

Earlier studies in China showed AUROCs of 0.790 and 0.873 for the FLI in detecting NAFLD [20,27]. In recent years, the FLI was additionally evaluated in multiple large-scale studies across various regions. The AUROC of one study involving 4247 participants in northern China was determined to be 0.87 [28]. Interestingly, the AUROC decreased to 0.72 in obese individuals, defined as having a BMI ≥28 kg/m^2. This may suggest limited application of the FLI in this group. For the other studies that involved 13,122 subjects in Sichuan (southwestern China), 3548 subjects in Shanghai (eastern China), 3259 subjects in Nanjing (eastern China) and 21,468 subjects in Zhejiang (eastern China), the AUROCs were 0.88, 0.76, 0.85 and 0.85, respectively, compared with ultrasound-diagnosed fatty liver disease [29–31]. Similar studies were also conducted in Korea and Japan, which showed corresponding AUROCs of 0.791 and 0.884 for FLI [32,33]. When the FLI is applied to patients with other comorbid conditions, its utility remains high. In a study that examined 364 Chinese patients diagnosed with hep B, the AUROC for the detection of NAFLD was 0.753 [34]. In another study that investigated the use of the same index in Chinese patients with sleep apnea, the AUROC was 0.802 [35].

Fatty Liver Disease Index

The FLDI was created as an alternative to the FLI and HSI to screen large populations for fatty liver disease in China. It incorporates four variables, BMI, triglycerides, ALT/AST ratio and presence of hyperglycemia, in the calculation of the final score. The cutoff was determined using the validation set in the original study, who were diagnosed by ultrasound. The FLDI achieved an AUROC of 0.81 with scores <28 excluding NAFLD with a sensitivity of about 95% and >37 in detecting NAFLD with a specificity of 96% [19].

The FLDI index was externally validated in two sizable studies in China. In one that examined 13,122 subjects receiving health check-ups in western China, the AUROC for detecting NAFLD was 0.874 [36]. A 2022 study by Zhang *et al.* analyzed 3259 patients from eastern China and determined the AUROC of the FLDI to be 0.852 [30]. The authors also found that the optimal cutoff for the FLDI was >28.7 based on the maximal Youden's J index, which would result in a sensitivity of about 80% and a specificity of 75%. This difference in AUROC when the FLDI is applied to individuals in different regions highlights the role of ethnogeography in the utility of the indices [29,30]. A possible explanation is attributed to varied lifestyles, as inhabitants in eastern China are known to have a higher prevalence of hypertension, a risk factor for NAFLD [37]. Lastly, in another study that examined Chinese patients with hep B, the AUROC for the detection of NAFLD was 0.780 [34].

Hepatic Steatosis Index

In 2010, the HSI was developed as a screening method through a large-scale cross-sectional study (n = 10,724) in Korea to determine whether patients should receive imaging follow-up for potential NAFLD [12]. This new tool was developed because researchers believed that the usage of the FLI could potentially be inappropriate, given that some of the primary variables (i.e., BMI, waist circumference) differed significantly between the original FLI derivation population (from Italy) and the Korean population. The HSI incorporates the following variables in its formula: ALT/AST ratio, BMI and type II diabetes mellitus. In the original study, when compared with ultrasound, the HSI had an AUROC of 0.812 (95% CI: 0.801–0.824). At scores <30.0, the HSI excluded NAFLD with a sensitivity of 93.1% and, at scores >36.0, the HSI detected NAFLD with a specificity of 92.4% [12].

When data were analyzed from 1300 adult patients at Wonkwang University Hospital in Iksan, Korea, the HSI showed an AUROC of 0.784 (95% CI: 0.758–0.809). The sensitivity was 71.5%, the specificity was 70.9% and the cutoff value was 33.2 [32]. A different study of 339 asymptomatic patients in Korea was performed to determine the accuracy of the HSI to diagnose NAFLD compared with nonenhanced CT imaging measures [38]. After excluding 55 patients, the HSI showed an AUROC of 0.775 (95% CI: 0.728–0.820), with a sensitivity of about 73% and a specificity of 74% at a cutoff value of 33.86 ($p < 0.001$) when measured against absolute liver attenuation on CT. The AUROC was 0.779 (95% CI: 0.730–0.822) with a sensitivity of 73.5% and a specificity of 76.3% at a cutoff value of 36.06 when measured against the liver-spleen attenuation ratio on CT. Finally, the AUROC for the HSI was 0.749 (95% CI: 0.699–0.794) with a sensitivity of 70.6% and a specificity of 76.0% at a cutoff value of 36.06 when measured against the attenuation difference between the liver and spleen on CT [38].

In a 2021 study including Japanese participants, NAFLD was diagnosed in 1935 (28.0%) of the 6927 subjects by ultrasound [33]. The AUROC of the HSI was 0.874. From the NAGALA study (a cross-sectional review of a Japanese health center by Hamaguchi and colleagues in 2019), a subset of data from 14,281 subjects, excluding patients with risk factors such as alcoholic fatty liver, substance abuse, viral hepatitis and diabetes, was selected to determine the validity of various indices for NAFLD [39]. The AUROC of the HSI was determined to be 0.8678 (95% CI: 0.8604–0.8752) with a specificity of 77.38% and a sensitivity of 80.22%.

When assessing the HSI in a retrospective cross-sectional study of 21,468 participants from China with ultrasound-diagnosed NAFLD, the AUROC was 0.828 (95% CI: 0.822–0.834) [31]. In another study in which validation of various fatty liver indices was performed in western China, data from 3122 patients (of which 2692 were NAFLD patients) were reviewed in a retrospective cross-sectional design and showed an AUROC of the HSI of 0.833 (95% CI: 0.825–0.841) [36]. In a coal mining community in northern China, 4247 adult participants were included in an external validation study of various liver indices, and the AUROC of the HSI was 0.83 (95% CI: 0.82–0.84), with the lower rates in obese participants [28]. In 2017, a cross-sectional study recruited 19,804 Chinese participants to originally review the accuracy of the ZJU index. NAFLD was diagnosed by clinical evaluation based on lab data and ultrasound, with the analysis showing an AUROC for the HSI of 0.854 (95% CI: 0.846–0.863) [27]. Additionally, when the HSI was tested in a population (n = 3548) of middle-aged and elderly Chinese patients in Shanghai, the index showed an AUROC of 0.77 with a cutoff of 33, sensitivity of 68% and specificity of 71% [29].

Additional studies also examined the effect of comorbid conditions on the utility of the HSI in detecting NAFLD. In the context of weight loss, the HSI showed a significant correlation with changes in fat fraction measured by magnetic resonance spectroscopy ($R^2 = 0.69$; $p < 0.001$), while the FLI did not show any correlation in a study of 39 living liver donors [40]. While the HSI was developed using an adult Korean population, a study showed that the index could also be useful to determine NAFLD in pediatric patients. Recently, a study of 1845 Chinese pediatric subjects was performed and the AUROC of the HSI for detecting NAFLD was 0.964 [41]. Obstructive sleep apnea/hypopnea syndrome (OSAHS) has also been correlated with obesity and higher BMI status. Since the calculation of various fatty liver indices often relies on obesity-related measures, Chen and colleagues recruited 431 patients from China to determine the validity of some of these indices [35]. In patients with OSAHS, the AUROC for the HSI was 0.753 (95% CI: 0.710–0.793). Lastly, a study explored the performance of noninvasive indices for NAFLD in patients with hep B infections [34]. A total of 364 Chinese patients with hep B viral infections, who underwent liver biopsies, were recruited and enrolled. The AUROC of the HSI in predicting hepatic steatosis in this cohort as diagnosed by biopsy was 0.627 (95% CI: 0.546–0.707).

Zhejiang University Index

The ZJU index was developed in 2015 to screen for NAFLD in a Chinese population, given that the development and validation of other noninvasive liver indices such as the FLI were primarily based on Western populations [20]. A cross-sectional matched-pair study of 9602 adult patients was performed at Zhejiang University, and the diagnosis of NAFLD was based on ultrasound examinations. The four variables used in the ZJU index are BMI, fasting plasma glucose, triglycerides and the ALT/AST ratio. In the derivation cohort, the AUROC of the ZJU was 0.822 (95% CI: 0.810–0.834). At a cutoff value of <32, the ZJU index excluded NAFLD with a sensitivity of 92.2% and, at a cutoff value of >38, the ZJU index detected NAFLD with a specificity of 93.4%. The validation cohort also showed a consistently high AUROC for the ZJU index at 0.826 (95% CI: 0.815–0.838). Compared with the gold-standard liver biopsy in 148 subjects for NAFLD diagnosis, the ZJU index AUROC was 0.896 (95% CI: 0.818–0.974). A study in a coal-mining community in northern China showed an AUROC of 0.87 (95% CI: 0.86–0.88) for the ZJU index [28]. When applied to a study of Chinese pediatric patients, the ZJU index had an AUROC of 0.960 for detecting NAFLD [41]. The most recent external validation study of 3259 subjects in Nanjing, China, showed that, compared with diagnosis by ultrasound, the ZJU index had an AUROC of 0.847 (95% CI: 0.835–0.860) [30]. Another study by Jung and colleagues showed that the AUROC of the ZJU was 0.69 compared with ultrasound in a population of 1301 Korean patients [23]. These results indicate that the use of the ZJU for populations other than Chinese adults may require specific stratification or possibly a different threshold cutoff.

Framingham Steatosis Index

The main aim of the initial study that established the FSI was to determine the best predictor of hepatic steatosis among ALT, AST and the more commonly used ALT/AST ratio [21]. A cross-sectional analysis of 1181 predominantly non-Hispanic white subjects from the Framingham Third-Generation Cohort was performed to determine the accuracy of ALT, AST and ALT/AST ratio. A regression analysis was performed to determine the FSI, which incorporates the following variables: age, sex, BMI, triglycerides, hypertension, diabetes and ALT/AST ratio. The C-statistic for the FSI in the derivation cohort was 0.845 with a sensitivity of 79% and a specificity of 71% at a cutoff point of 23. A cohort of 4489 patients from the NHANES III study was used to validate the FSI, and this validation cohort showed a C-statistic of 0.760 for the FSI [21]. Noteworthy, the FSI has not been widely studied in the context of East Asian populations, and data from existing literature varies. One study showed that the FSI had an AUROC of 0.85 (95% CI: 0.84–0.86) in detecting NAFLD when 4247 Chinese patients were examined [28]. However, a study by Jung *et al.* showed that the FSI only had an AUROC at 0.70 when applied to 1301 Korean patients [23]. Therefore, more studies are required to fully elucidate the utility of this index.

Discussion

The rising prevalence of NAFLD worldwide raises the need for a cost-effective screening tool to identify those at risk. This would be followed by prompt diagnosis and management before the disease progresses to an irreversible stage. Noninvasive liver indices are advantageous as they are cost-effective and can be administered over a large, asymptomatic population, in contrast to traditional diagnostic tools such as liver biopsy. However, many of the indices have not been validated externally in the East Asian population subgroups, which have different cutoff thresholds for BMI and waist circumference due to genetic and environmental factors [42]. In this review, we compared the accuracy of the indices against one another in different validation studies (Table 2).

In general, the FLI, which is the most validated test to date, showed the highest accuracy in detecting NAFLD in East Asian patients in multiple studies. This is significant as the population characteristics (age, ethnicity, size) and diagnostic modality (US, CT or MRI) of the study populations were variable, yet the FLI consistently performed better. A major limitation of FLI is that it was originally created to detect fatty liver disease diagnosed by ultrasonography, instead of the gold-standard liver biopsy. This could have an impact on the overall sensitivity and specificity of the test. Furthermore, it cannot quantify the severity of hepatic steatosis, which would provide valuable information in selecting the most appropriate treatment for the patient. Of note, a meta-analysis by Castellana and colleagues that aggregated validation studies of the FLI in different countries concluded that the index has a weak diagnostic performance. This supports the use of the FLI as an initial screening tool to identify at-risk individuals for further workup [13].

Another index that had a reliable performance in detecting NAFLD is the ZJU index. Being one of the new indices, the ZJU shares two variables in its algorithm with the FLI: BMI and triglyceride levels. The other two components involve the ALT/AST ratio and fasting glucose levels. This may be a better model as the Asian population typically has a smaller waist circumference, which is used in FLI calculation [20]. The ZJU index was also designed initially using ultrasound diagnosis in the original study instead of liver biopsy, which is the gold standard, a potential limitation to its application.

The FLDI has only been validated in Chinese patients, so its generalizability in screening for NAFLD remains uncertain. However, it may be appropriate in patients with hep B infection, as it had the best accuracy compared with the FLI and HSI in one study. We included the study with hep B infection to examine whether liver indices still have high predictive value in populations with pre-existing liver conditions, compared with a more randomly selected patient cohort. This is important as hep B disproportionately affects Asian Americans, according to the data from the Centers for Disease Control. This raises the potential to stratify the use of the index for different subpopulations within the overall Asian demographics and achieve an individualized approach to screening management.

Table 2. Cross-comparison of fatty liver indices in populations examined with respect to diagnostic tool used to determine nonalcoholic fatty liver disease diagnosis.

Study (Year)	Population (n)	Diagnosis method	AUROC (95% CI)					Ref.
			FLI	HSI	ZJU	FSI	FLDI	
Lee *et al.* (2010)	Korean adults (derivation cohort; n = 10,724) Korean adults (validation cohort; n = 5364)	US	0.783 0.786	0.812 (0.801–0.824) 0.819 (0.808–0.830)				[12]
Wang *et al.* (2015)	Chinese adults (derivation cohort; n = 4800) Validation cohort (n = 4802) Second validation cohort (n = 148)	US US Liver biopsy	0.790 (0.778–0.803)	0.793 (0.781–0.806)	0.822 (0.810–0.834) 0.826 (0.815–0.838) 0.896 (0.818–0.974)			[20]
Zhang *et al.* (2016)	Chinese hepatitis B patients (n = 364)	Liver biopsy	0.753 (0.674–0.832)	0.627 (0.546–0.707)			0.780 (0.708–0.852)	[30]
Xia *et al.* (2016)	Chinese adults (n = 3548)	US	0.76 (0.74–0.77)	0.77 (0.75–0.78)				[29]
Li *et al.* (2017)	Chinese adults (n = 19,804)	Lab data + US	0.873 (0.866–0.881)	0.854 (0.846–0.863)	0.925 (0.919–0.931)			[27]
Shen *et al.* (2017)	Chinese adults (coal-mining community; n = 4247)	US	0.87 (0.86–0.88)	0.83 (0.82–0.84)	0.87 (0.86–0.88)	0.85 (0.84–0.86)		[28]
Zhu *et al.* (2018)	Chinese adults (n = 13,122)	US	0.880 (0.874–0.886)	0.833 (0.825–0.841)	0.861 (0.854–0.868)	0.864 (0.857–03871)	0.874	[36]
Chen *et al.* (2019)	Chinese sleep apnea patients (n = 431)	US	0.802 (0.762–0.839)	0.753 (0.710–0.793)				[35]
Cen *et al.* (2020)	Chinese adults (n = 21,468)	US	0.849 (0.843–0.855)	0.828 (0.822–0.834)				[31]
Jung *et al.* (2020)	Korean adults (n = 1301)	MRI	0.68 (0.64–0.71)	0.69 (0.66–0.73)	0.69 (0.66–0.72)	0.70 (66–0.73)		[23]
Murayama *et al.* (2021)	Japanese adults (n = 1935)	US	0.884 (0.876–0.892)	0.874 (0.865–0.883)	0.886 (0.877–0.894)			[33]
Shi *et al.* (2021)	Chinese pediatric patients (n = 1845)	US		0.964	0.960			[41]
DiBattista *et al.* (2022)	American adults (n = 701)	Imaging from EMR (US, CT or MRI)		0.76 (0.72–0.79)		0.78 (0.74–0.82)		[43]
Han and Lee (2022)	Korean adults (n = 1300)	CT	0.791 (0.766–0.816)	0.784 (0.758–0.809)	0.704 (0.675–0.734)			[32]
Zhang *et al.* (2022)	Chinese adults (n = 3259)	US	0.852 (0.839–0.864)		0.847 (0.835–0.860)		0.852 (0.839–0.864)	[30]

AUROC: Area under receiver operating curve; CT: Computed tomography; EMR: Electronic medical records; FLDI: Fatty Liver Disease Index; FLI: Fatty Liver Index; FSI: Framingham Steatosis Index; HSI: Hepatic Steatosis Index; US: Ultrasound; ZJU: Zhejiang University Index.

As NAFLD incidence continues to rise, early detection and management are important to change the course of the disease progression in patients, especially among high-risk patients. In large populations with varying access to healthcare, noninvasive screening tools like liver indices remain immensely useful to help identify cases of NAFLD. While the most used liver index is the FLI, there has been debate in the scientific community as to whether the FLI is generally applicable to non-Caucasian populations, since it was primarily developed based on an Italian population with most validation studies having been performed in the USA. Recognizing that population health trends vary widely between Western and East Asian populations, these differences in population health metrics may impact screening factors within the FLI. Thus, several new liver indices have emerged, attempting to capture more accuracy, especially in East Asian subgroups, which experience a higher incidence of NAFLD at leaner BMIs.

Conclusions

The development and validation of the presented liver indices (FLI, FDLI, HSI, ZJU, FSI) highlight the heterogeneity in sensitivity and specificity of the NAFLD screening markers. While the FLI performed well overall, other liver indices may be more suitable in select groups. For instance, in Chinese pediatric patients, the HSI was able to more accurately screen NAFLD. Nevertheless, the number of studies examining the utility of liver indices in the pediatric population remains scarce. Chinese adults with fatty liver diseases screened by the ZJU and FLI indices show comparable accuracy, yet the FLI was able to yield better result for the obstructive sleep apnea-hypopnea syndrome (OSAHS) group within this population. These results demonstrate a need to consider stratifying the use of liver indices for different subgroups within the Asian population and additional studies are required to understand these different factors at play. Lastly, research involving East Asian American populations will be useful to clarify the clinical pathophysiology of NAFLD in leaner BMIs of East Asian populations in relation to inherited or environmental factors contributing to the disorder.

Future perspective

The global epidemic of obesity and metabolic syndrome could be the underpinning of the growing global prevalence of NAFLD. The strong association between NAFLD and features of metabolic syndrome, obesity and Type 2 diabetes demonstrates the importance of early screening for NAFLD among patients with cardiovascular diseases. With a high cardiometabolic disease burden, the clinical utility of liver disease indices becomes of paramount significance to mitigate new liver disease onsets, especially among high-risk population groups. Despite their increased NAFLD risk, the representation of Asian subgroups in the validation of liver disease indices is limited. Engaging Asian subgroups in developing new liver disease indices or validating existing ones is needed. Additionally, large trials that investigate the incidence of NAFLD among patients with different cardiometabolic risk profiles could inform prevention or treatment strategies to reduce disease risk in high-risk Asian subgroups.

Executive summary

Background

- Nonalcoholic fatty liver disease (NAFLD) is prevalent and poses a significant public health concern in the USA.
- Accessible liver indices as screening tools are needed to identify individuals at risk of developing NAFLD.

Methods

- No uniform guideline exists for the use of liver indices in patients of East Asian descent who present with distinct anthropometric characteristics.
- This review analyzed retrospective validation studies of five liver indices in different Asian population cohorts and compared their overall accuracy.

Results

- The Fatty Liver Index is the best externally validated and had the highest accuracy in detecting NAFLD in multiple studies.
- Other liver disease indices yielded superior results in select patient populations such as hepatitis B and obstructive sleep apnea patients.

Future perspective

- More validation studies are needed to investigate the clinical utility of applying NAFLD indices to Asian American subgroups.
- Trials that investigate the incidence of NAFLD among patients with different cardiometabolic risk profiles could inform prevention or treatment strategies to reduce disease risk in high-risk Asian subgroups.

Disclaimer

The views and opinions presented here represent those of the authors and should not be considered to represent advice or guidance on behalf of the US FDA.

Financial & competing interests disclosure

This work was partly supported by the CTSA (UL1TR002649 from the National Center for Advancing Translational Sciences) and the CCTR Endowment Fund of Virginia Commonwealth University. YM Roman is an employee of the US FDA. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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