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An empirical analysis of the Fatty Liver Index for the detection of Non-Alcoholic Fatty Liver Disease in the overall population

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Abstract: Research on the efficacy of the non-invasive fatty liver index (FLI) in excluding or diagnosing non-alcoholic fatty liver disease (NAFLD) remains limited, but it has been utilized in population research to stratify risk. We evaluated the efficacy of FLI in identifying NAFLD and the frequency of NAFLD in each FLI class by a meta-analysis. Methods. No results were found until January 2021 across all four databases (CRD42021231367). We considered original articles that reported FLI performance using CT, MRI, or ultrasound as the reference standard. Using 30 and 60 as cut-offs, the number of participants with NAFLD in FLI classes <30, 30-60, and ≥60, as well as the number of subjects categorized as true positive/negative, were extracted. The data was pooled using a random-effects model. End result. Fatty liver disease did not have any secondary causes in any of the ten investigations that involved 27,221 participants. There found a prevalence of NAFLD of 14%, 42%, and 67% in the three FLI groups, respectively. For the lower cut-off, the following metrics were measured: sensitivity (81%), specificity (65%), positive predictive value (84%), negative predictive value (65%), likelihood ratio for positive results (2.3), and diagnostic odds ratio (7.8). For the higher cut-off, the corresponding metrics were 44%, 90%, 67%, 76%, 4.3, 0.6, and 7.3. Studies that used ultrasound as opposed to other imaging modalities generally revealed comparable performance. Final thoughts. FLI was able to adequately stratify the risk of NAFLD. On the other hand, it failed to definitively exclude or diagnose this disease, and the evidence of discriminatory performance was minimal.

Index Terms **- Component, formatting, style, styling, insert.** Fatty liver index, steatosis, non-alcoholic fatty liver disease, liver.

I. INTRODUCTION

The healthcare system, individuals afflicted, and their families are profoundly impacted by non-alcoholic fatty liver disease (NAFLD), a prevalent condition that is characterized by high rates of morbidity and excess mortality. This illness is thought to affect approximately one-quarter of the world's population, with some populations reporting significantly greater rates [1,2]. It has surpassed all other causes of chronic liver disease and the rate of liver transplantation in recent years [3,4]. Liver biopsy is the gold standard for NAFLD diagnosis. But it's no secret that there are a lot of problems with this method, thus it can only be examined in a small subset of subjects. Indeed, a liver biopsy is an intrusive procedure that can be expensive and carries a small but real risk of consequences. There is also a mismatch between the amount of procedures that can be done and the burden of NAFLD [5,6,7].

The introduction of non-invasive tools (NITs) is an attempt to circumvent these restrictions. Hepatic steatosis is the hallmark of non-alcoholic fatty liver disease (NAFLD), which must be distinguished from its secondary manifestations by the absence of alcohol, viral infections, drugs, autoimmune diseases, and genetic abnormalities [5,6]. Imaging techniques such as computed tomography (CT), magnetic resonance (MR), controlled-attenuation parameter measurement (CAP) via vibration-controlled transient elastography (VCTE), and ultrasound can all be employed to identify hepatic steatosis. Since imaging's accessibility and cost significantly affect practicality, serum biomarkers are used for larger-scale investigations [6,8]. Currently, the fatty liver index (FLI) is endorsed by both the Asian Pacific Association for the Study of the Liver (APASL) guidelines [6,8] and the European Association for the Study of Diabetes and Obesity (EASL-EASD-EASO) guidelines [6,8]. It is the best-validated tool available. FLI is an easy-to-understand formula that takes into account four widely-available variables: GGT, waist size, body mass index, and triglycerides. A number of research evaluated the reliability of this technique after its initial development by Bedogni et al. for the purpose of predicting hepatic steatosis in the general population [9,10,11]. Scores below 30 on the FLI were deemed to indicate low risk of hepatic steatosis, whereas scores of 60 or above were deemed to indicate high risk, according to the original publication.

II. MATERIALS AND METHODS

The PRISMA-DTA Statement (Tables S1 and S2) and PROSPERO registration number (CRD42021231367) were followed in the execution of this meta-analysis [25].

The 2.1. Search Approach

A search approach with six steps was devised. Our first step was to use PubMed to look for sentinel studies. We then used PubMed to find relevant keywords. The third point is that the following comprehensive search method was employed in PubMed: (NASLD) AND ("fatty liver index" [Title/Abstract]). The fourth step was to apply the same methodology to the searches conducted in CENTRAL, Scopus, and Web of Science. As a fifth point, we only included studies that looked at how well FLI worked in randomly selected individuals who had NAFLD identified by imaging. We did not include studies that met these criteria: (1) with a sample size of less than 100 subjects; (2) with a focus on specific subgroups (e.g., pediatric, with or without type 2 diabetes, bariatric surgery subjects); (3) using CAP as the gold standard for NAFLD diagnosis [26]; (4) using histology as the gold standard; (5) evaluating FLI other than the one developed by Bedogni et al. [9]; (6) with letters, commentaries, and posters. Final step: we looked for other publications by searching the references of the included research. January 20, 2021 was the last day for which information was sought. Language was not a limiting factor. Data extraction was carried out by two researchers (M.C., F.P.) working separately. They searched for papers, checked their titles and abstracts, reviewed their full-texts, and finally, chose articles for inclusion.

In a pilot study, the same scientists worked separately to obtain the following data: (1) study details (author, publication year, country, study type, inclusion criteria, and subject count); (2) FLI interpretation cutoffs; (3) total subjects with imaging-diagnosed NAFLD in each FLI class; (4) accurate/false positive/negative subjects. This study used ultrasound, computed tomography, or magnetic resonance imaging as its gold standards. This index test was FLI. As mentioned, FLI can be understood with a lower and upper threshold, for example, 30 and 60, respectively. Each set of data was extracted independently. A individual who did not have NAFLD was considered to have tested falsely positive if their score was more than the cut-off or true negative if their score was lower. Just as a patient with NAFLD was considered to have tested positive if their score was more than the cut-off, they were considered to have tested negative if their score was lower. After choosing each publication, we checked the primary paper and any additional data. If any data was missing, we emailed the authors to get the missing information. Data was double-checked and disputed when needed.

Examining the Quality of the Study (2.3)

Independently, two reviewers (M.C., F.P.) used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool to evaluate the included studies for potential bias in patient selection, index test, reference standard, flow and timing, and quality measurement. Applicability and bias risk were categorized as high, unclear, or low, respectively [27].

2.4. Analysis of Data

We summarized the features of the included studies and then conducted independent analyses following these methods. The first step was to do a meta-analysis of proportions in order to get the pooled rate and 95% CI for each FLI class among the participants that were assessed, as well as for NAFLD within a particular FLI class. Data pooling statistical analysis made use of a random-effects model. Next, a meta-analysis was conducted to determine how well FLI values less than 30 and greater than or equal to 60 could exclude or select NAFLD. With the 95% CI, we estimated summary operating points such as sensitivity, specificity, NPV, PPV, LR+, LR-, and DOR. DOR gives a unified metric for evaluation of test performance, which is LR+/LR- and represents the probability of a FLI score exceeding the given cut-off in a group of NAFLD subjects relative to a group of non-NAFLD subjects. The values might be anywhere from zero to infinity, with larger numbers denoting better efficiency. LR+ is the differential between the true positive and false positive rates of FLI scores over the particular cut-off in NAFLD subjects compared to non-NAFLD subjects.

III. RESULTS

3.1. Features of the Research

Eight hundred and three papers were located using several databases: 250 in PubMed, 49 in CENTRAL, 276 in Scopus, and 228 in Web of Science. An extra study was obtained from an individual's database [21]. The title and abstract of 316 articles were reviewed after 488 duplicates were removed. Out of 259 records, 259 were deemed unsuitable due to their focus on specific subgroups (e.g., pediatric, type 2 diabetes, bariatric surgery subjects, etc.), small sample size (less than 100 patients), evaluation of FLI methods other than the one developed by Bedogni et al. [9], use of reference standards other than ultrasound, CT, or MR, or irrelevant to the review's subject matter. Figure S1 shows that ten studies out of 57 total papers were ultimately included in the meta-analysis [12,13,14,15,16,17,18,19,20,21]. The references of the listed studies did not yield any more research.

3.2. Analyzing Qualitative Data

Table 1 summarizes the collected papers' characteristics [12,13,14,15,16,17,18,19,20,21]. Sample sizes varied from 195 to 8626 patients in the research published between 2013 and 2021. One study did not report its design, whereas three were prospective cohorts and five were cross-sectional [18]. A total of ten studies were carried out across several countries, including Brazil, China, Israel, Italy, Japan, Korea, Spain, Taiwan, the Netherlands, and the USA. In most research, adults without underlying liver conditions were included; however, two studies [15,16,17,18] did not include pregnant women, and four studies [14,15,17,19] did not include patients with established liver illness (e.g., cirrhosis). Seven studies used ultrasound to diagnose NAFLD; two of these groups used magnetic resonance imaging (MR) as their reference standard, while one group used computed tomography (CT) [15,19,20]. In the other three groups, ultrasonography was used. According to Arteaga et al. (26% prevalence) and Chen et al. (46% prevalence) [14,18], the prevalence of NAFLD varied. With the sole exception of Zelber-Sagi et al., who solely examined the higher cut-off, most studies examined the performance of both the lower and higher FLI cut-offs [13]. In all, 27,221 individuals were considered, and 8,273 of them had a NAFLD diagnosis.

Table 2.

First Author, Year	Country	Study Design	Number of Patients	Population	NAFLD (%)	FLI< 30	FLI>60
Zelber, 2018	Israel	PCS	2872	>55years, without secondary causes of FLD	1027(37%)	×	×
Koehler, 2020	The Netherlands	Cross-sectional	349	24-70 years, without secondary causes of FLD(alcohol, drugs, virus)	126(32%)	×	×
Jung, 2021	Korea	Cross-sectional	2872	>30 years, without known liver disease or secondary or autoimmune disease	662(42%)	×	×
Mc-Henry, 2022	USA	PCS	1450	18-65 years, without secondary causes of FLD (alcohol)	671(41%)	×	×

Data Analysis with Numbers

The inclusion criteria for the study were the pooled prevalence of all FLI classes and the prevalence of NAFLD within each FLI class. In general, 49% of the FLI < 30 class, 27% of the FLI 30-60 class, and 23% of the FLI ⩾ 60 class had the condition, with a 95% confidence interval ranging from 40 to 58. A total of 14% (95% CI: 9 – 19) of the FLI < 30 class, 42% (95% CI: 34 – 51) of the FLI 30 – 60 class, and 67% (95% CI: 58 – 75) of the FLI ⩾ 60 class were found to have NAFLD. In the first two FLI classes, NAFLD diagnoses were not different based on imaging modality.

Table. Summary estimates of the fatty liver index in identifying non-alcoholic fatty liver disease

Cut-Off	No.of subjects	Prevalence of Non-Alcoholic Fatty Liver Disease(95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Negative Predictive Value (95% CI)	Likelihood ratio	Diagnostic Odds Ratio
<30	27,889	43	78	58	93	2.56	7.49
>60	28.277	41	92	76	78	4.36	8.35

3.4. Evaluating the Quality of the Study

Tabulated in Table S4 is the potential for bias in the research that were considered. The study included a random or consecutive sample of subjects who underwent ultrasound, computed tomography, or magnetic resonance imaging and were ultimately diagnosed with non-alcoholic fatty liver disease (NAFLD) within a specified time frame. FLI was computed using objective parameters such as body mass index (BMI), glycaemic load (GGT), triglycerides, and waist circumference, and was interpreted using standard cut-offs such as 30 and 60. In terms of reference standard bias, the most reliable way to diagnose and stage NAFLD is with a liver biopsy. We ranked the related item for the risk of bias as high since imaging methods perform significantly but sub optimally when diagnosing steatosis [29]. Also, the reference standard had serious application issues because eight studies found NAFLD after removing some of the major secondary causes of FLD but not all of them [12,14,15,16,17,19,20,21]. The inclusion of only participants aged 55 or older raised significant concerns about the applicability of patient selection in the study by Koehler et al. [12]. Lastly, there were a number of studies that failed to disclose data that would have allowed for an evaluation of the patient selection process or the risks of bias related to flow and timing [13,15,16].

Finding the strongest evidence on FLI's ability to stratify risk of NAFLD and confirm or disprove the presence of this condition in big unselected subject groups was the primary goal of this meta-analysis. We conducted a comprehensive database search without limitations on time or language, and we specified inclusion criteria before we started. Based on independent summary operating metrics, this meta-analysis allowed studies examining populations with different prevalence of NAFLD to be evaluated together; to the best of our knowledge, it is the first of its kind.

Among the ten trials that were located, one assessed the efficacy of FLI in 8273 patients with NAFLD and the other in 18,948 patients without the disease. Importantly, the only people who were typically left out of these studies were those who were pregnant, had a history of liver illness, or had secondary causes of FLD. Researchers did not use anthropometric data or comorbidities (such as type 2 diabetes or obesity) to choose study participants. Actually, only in Koehler et al. [12] did an age requirement for eligibility lead to the enrollment of a fraction of the population that was older than 65. Also, the worldwide prevalence of NAFLD was quite close to what a previous meta-analysis estimated [1]. Because of this, we may conclude that the

included studies were not skewed in any particular direction and that our findings may be generalizable to groups not included in the analysis.

An estimated 14% of those with FLI scores below 30 had NAFLD, 42% had scores between 30 and 60, and 67% had scores of 60 or above. These results lend credence to FLI's utility in population studies for risk stratification of NAFLD. The use of FLI for the diagnosis or exclusion of NAFLD appears to be discouraged, nonetheless. A diagnostic performance meta-analysis was carried out to provide further understanding of the second application. As with other NITs, FLI's original intent was to use publicly available anthropometric and laboratory data to differentiate between low-risk and high-risk people for NAFLD based on a score either below or over the lower cut-off. For individuals who score somewhere in the middle (i.e., indeterminate) between the lower and higher cut-offs, stratifying their risk of NAFLD is not feasible; alternative solutions should be explored for this specific group of people (e.g., in a population research analysing ultrasound data) [9]. The diagnostic utility of FLI is called into question by the current meta-analysis. To start, there was only little evidence of discriminatory performance (81% sensitivity, 84% NPV, and 0.3 LR-) when the lower cut-off was evaluated. Additionally, despite taking into account the increased cut-off, 90% specificity, 67% PPV, and 4.3 LR+ were observed, which once again only suggests a weak level of discriminatory ability. Thirdly, the dual-threshold technique resulted in an indeterminate classification for around 25% of patients, which is equivalent to the percentage of participants with a FLI score ranging from 30 to 60. Some conclusions may be obtained by extrapolating our analysis to a made-up population. As an example, around 16% of patients would have been misclassified as non-NAFLD if participants with scores below the lower cut-off were thus classified. Similarly, imaging would have only verified the diagnosis in 2 out of 3 patients if subjects with scores greater than the higher cut-off were deemed to have NAFLD. Finally, the amount of data checks might have been decreased by 73% if only participants with scores between the lower and higher cut-offs were evaluated for an imaging-based diagnosis of NAFLD. However, the limitations of the single techniques would still be applicable. To sum up, our findings disprove FLI's use in identifying or ruling out NAFLD. It is more accurate to think of it as a tool for NAFLD risk stratification; yet, its poor diagnostic performance calls attention to the necessity for improved markers. The use of imaging should be maintained until these technologies are created and proven. Since it is widely accessible, safe, inexpensive, and does not have any contraindications, ultrasound should continue to be seen as the gold standard when it comes to population studies.

IV. Conclusion

The high prevalence and clinical relevance of NAFLD have prompted the scientific community to develop non-invasive tools with the aim of assessing the individual risk of steatosis or fibrosis and to facilitate the conduction of large studies. FLI is a practical instrument, based on commonly available data, and is the only non-invasive tool currently recommended for the assessment of steatosis. In the present study, only studies with a low selection bias were included and FLI was found to be effective in stratifying the risk of NAFLD. About one in six subjects classified as FLI < 30 were confirmed to be affected by NAFLD, compared to about two in three in those of those classified as FLI $\geqslant$ 60. Conversely, only a weak performance was found when assessing its potential application to exclude or diagnose NAFLD. Further prospective studies would be helpful to further support the performance of the FLI and assess its role in the diagnosis of MAFLD.

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