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Hepatic fibrosis in morbidly obese patients: fibroscan accuracy

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Abstract

Metabolic associated steatotic liver disease (MASLD) stands as the most common hepatic disorder in both developed and developing countries. The global increasing rates in obesity rates are fuelling an increase in MASLD cases. Fibroscan, a transient elastography device, is a research-based, noninvasive method for assessing liver fibrosis. Accurately measuring the extent of fibrosis presents difficulties in a cohort of individuals who are severely obese with a body mass index (BMI) ≥ 40 kg/m^2, particularly regarding the reliability and applicability of the XL probe. This study's objective is to evaluate the precision of fibroscan in morbidly obese individuals with a BMI ≥ 40 kg/m^2. We explored Google, PubMed, and Medline to gather information on fibroscan and its application for measuring fibrosis levels in morbidly obese patients ≥ 40 kg/m^2 who have MASLD. The fibrosis levels obtained from the fibroscan do not consistently correlate with the clinical or histopathological data, which are essential for accurately determining liver stiffness measurement (LSM) cutoff values and/or ranges for these patients with either significant or advanced fibrosis. Additional prospective multicenter studies are necessary to better establish LSM cutoff values and/or ranges for patients suffering from significant or advanced fibrosis due to morbid obesity.

Keywords

Metabolic associated steatotic liver disease, fibroscan, fibrosis in morbidly obese patients, cutoff values for either significant or advanced fibrosis

Introduction

With an estimated prevalence of 20–40%, metabolic associated steatotic liver disease (MASLD) is the most prevalent liver disease in both developed and developing nations [1–3]. In several of these countries, it is also anticipated to take priority over other indications for liver transplantation. Simple steatosis, metabolic associated steatohepatitis (MASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) are

among the illnesses that comprise MASLD [4]. According to estimates, 6% to 13% of patients with simple steatosis go as far as developing steatohepatitis, and 10% to 29% of those patients develop liver cirrhosis within ten years [5].

Body mass index (BMI) of 30 or higher for non-Asians and 27.5 or higher for Asians was used to define obesity. A waist circumference of 102 cm or more for men and 88 cm or more for women was considered abdominal obesity. These metrics are unable to evaluate adiposity or body fat directly. Obesity and adiposity measures showed an increasing trend, despite differences between racial or ethnic groups. Between 2011 and 2018, there was a decline in lean mass and a leveling off in all measures of adiposity among non-Hispanic black individuals in a series of nationally representative cross-sectional surveys conducted in the United States. Non-Hispanic Asians showed increases in all measures, while non-Hispanic White and Hispanic individuals showed increases in waist circumference and BMI but no changes in body fat percentage or lean mass [6].

Globally rising obesity rates are contributing to a surge in the prevalence of MASLD, affecting up to 30% of the general population, 80% of those who are obese [7, 8], and 90% of patients undergoing bariatric surgery who have morbid obesity [9]. By 2030, 20% of adults are expected to be obese, and 40% will be severely obese (BMI ≥ 35 kg/m^2) [10]. In the morbidly obese population, men who smoke, have a higher BMI and are more likely to have advanced MASLD [11].

Fibroscan is an evidence-based transient elastography (TE) tool used for noninvasive evaluation of liver fibrosis and steatosis [12]. It measures the controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), which are useful for determining the degree of steatosis and liver fibrosis, respectively. The LSM measures the shear wave velocity of a push pulse through liver tissue. The shear wave travels more swiftly through hard liver tissue than through normal liver tissue, as was first noted by Yoneda et al. [13]. Based on new findings, individuals with mild portal hypertension (HTN) and compensated cirrhosis might benefit from bariatric surgery [14] since it could eliminate the underlying cause of their liver disease.

Specific patients' subsets

The incidence of major adverse cardiovascular events (MACE) is on the rise among young adults in the United States. There is a noteworthy correlation between the obesity pandemic among this demographic and the likelihood of MACE occurring. MASLD prevalence increased from 9.98% in 1999 to 19.49% in 2018, with a statistically significant trend. 5.29% and 9.52%, respectively, of patients have advanced and clinically significant fibrosis. Of young adults with MASLD, only 5% and 18%, respectively, had diabetes and HTN [15]. Compared to people without MASLD, young adults with MASLD had a marginally non-significantly higher prevalence of MACE. Nonetheless, about 40% of all deaths in MASLD patients are attributable to cardiovascular disease (CVD) mortality [16].

Women and smokers show a lower likelihood of being diagnosed with MASLD, with earlier research suggesting that the protective role of estrogen in pre-menopausal women contributes to this reduced risk of MASLD [16].

Only 29.29% of young adults with MASLD exhibited metabolic dysfunction, suggesting that the increased likelihood of MASLD may be associated with metabolically healthy obesity (MHO) status. MHO represents a distinct category of obesity that is more commonly observed in younger individuals who do not exhibit significant metabolic dysfunction despite being obese [17, 18]. This condition has been linked to an elevated risk of MASLD, indicating that hepatic fat may not merely be incidental but could serve as a systemic contributor to other metabolic diseases.

Our objective is to assess the accuracy of fibroscan in determining the degree of fibrosis in patients suffering from morbid obesity, specifically those with a BMI of 40 kg/m^2 or higher.

Methodology

A PubMed Mesh search was done using the following keywords, to find the peer-reviewed published articles which discussed the relation between the hepatic fibrosis measurement by fibroscan using XL probe in patients who are morbidly obese with BMI > 40 kg/m^2 without limitation of time:

Search: ("hepatic fibrosis" [Mesh]) OR ("liver fibrosis" OR "fibrosis degree") OR ("Non-invasive hepatic fibrosis methods") AND ("fibroscan") OR ("XL probe") OR ("morbid-obesity > 40 kg/m^2").

Also, we searched the Medline and Google using the following keywords: fibroscan, XL probe, fibrosis degree, morbid obesity, BMI > 40 kg/m^2, MASLD/MASH, and bariatric surgery.

The inclusion criteria include obese patients over 18 years of age with BMI ≥ 40 kg/m^2 who are preparing for bariatric surgery with MASLD or MASH and who undergo fibroscan to measure the fibrosis degree using XL probe. English peer-reviewed published articles during the last 20 years were included.

Exclusion criteria were as follows: individuals who have revision surgery or participate in two-stage procedures; alcohol intake exceeding 30 grams per day for males and 20 grams per day for females; confirmed infections of hepatitis B or C; liver conditions resulting from alternative causes, including autoimmune liver disease and metabolic storage disorders; current treatment with medications that contribute to fatty liver or enhance insulin sensitivity, such as estrogen, tamoxifen, amiodarone, methotrexate, and glitazones; assessment utilizing the M probe, patients with BMI < 40 kg/m^2 and non-English articles.

Only 6 articles fit the inclusion criteria (Table 1).

Table 1. Diagnostic accuracy for liver fibrosis in patients with MASLD using only XL probe

Author	Year	*N*	Probe	AUROC [prevelance (%)]			
				Stage 1	Stage 2	Stage 3	Stage 4
Friedrich-Rust et al. [19]	2010	50	XL	---	0.81 (30)	0.84 (24)	0.95 (6)
Friedrich-Rust et al. [20]	2012	43	XL	---	0.82 (n.d.)	0.84 (n.d.)	0.93 (n.d.)
Wong et al. [21]	2012	184	XL	---	0.80 (45)	0.85 (29)	0.91 (13)
Chan et al. [22]	2017	57	XL	---	0.90 (23)	0.95 (14)	0.97 (5)
Oeda et al. [23]	2020	96	XL	---	0.787 (52)	0.806 (27)	0.970 (5)
Cardoso et al. [24]	2020	81	XL	---	0.80 (19)	---	---

AUROC: area under the receiver operating characteristic curve; MASLD: metabolic associated steatotic liver disease. *N*: the number of patients; n.d.: not described; ---: no data. This table is adapted from Oeda et al. [25] (CC BY 4.0)

Non-invasive fibrosis assessment in MASLD

Hepatic fibrosis can be measured by different means either by serum fibrosis biomarkers or imaging techniques. Compared to liver biopsy, the gold standard for hepatic fibrosis measurement, serum fibrosis biomarkers are less expensive, have a low chance of sampling error, and can be performed repeatedly, making it possible to track fibrosis. While several panels, including the fibrosis 4 index, non-alcoholic fatty liver disease (NAFLD) fibrosis score (NFS), and BARD index, typically exhibit limited diagnostic precision for detecting advanced fibrosis, they remain valuable in clinical settings for excluding the presence of advanced fibrosis due to their elevated negative predictive values (NPVs) (exceeding 90%) [26]. A prime illustration of the continual advancements in serum biomarker panels is the BARDI score, an upgraded version of the BARD score that integrates the international normalized ratio (INR) into the assessment. By maintaining the simplicity and accessibility that rendered the BARD a fairly effective screening tool, the BARDI offers improved accuracy over the original BARD score without substantial additional costs [27].

Many predictive models have been postulated that mix between fibroscan and blood chemistry such as FibroScan-AST (FAST) [28] and Kao et al. [29] score. Recently, Ali et al. [30] postulated FibRO-3 (fibrosis risk score in the morbidly obese-3) model that adds hemoglobin A1c (HbA1c) (%) and alkaline phosphatase (ALP) (U/L) to LSM (kPa). This model demonstrated greater sensitivity in identifying fibrosis stage 2 when

compared to the FAST score, while its accuracy was on par with that of the FAST score. The ROC area for the FibRO-3 model exhibited statistically significant improvements over both the FAST and the Kao et al. [29] scores. Imaging modalities offer a more precise assessment of the fibrotic regions in the liver compared to serum biomarker assessments. Two distinct imaging methods for evaluating liver fibrosis or stiffness are magnetic resonance elastography (MRE) and ultrasound elastography techniques [31]. Both methods can offer additional details regarding the coexistence of hepatic steatosis by using the computed proton-density fat fraction (PDFF) with MRE or the CAP with vibration-controlled TE (VCTE), respectively [31, 32].

Disparities between fibroscan and alternative imaging techniques

According to reports, MRE and ultrasound elastography are valuable methods for diagnosing MASLD. MRE's area under the receiver operating characteristic curve (AUROC) value is higher than fibroscan's [33, 34], but its implementation is more expensive. In a head-to-head study directly comparing the diagnostic ability of MRE and VCTE in biopsy-proven MASLD patients, MRE is showing the best diagnostic accuracy regarding intra/interobserver reproducibility and stage 4 detection. MRE has several advantages over VCTE, including excellent diagnostic accuracy and a larger sampling area, whereas the main disadvantage of MRE compared with VCTE is the higher cost [35]. Recent studies have demonstrated the feasibility of MRE in children and adolescents [36–38], and it has been successfully used in a wide range of patient populations, including those with obesity, ascites, and unconventional hepatic anatomy [32]. Furthermore, even before frank fibrosis develops, MRE can identify slight increases in liver stiffness linked to inflammation and steatohepatitis, making it easier to distinguish between MASLD and MASH [39, 40]. In clinical environments, ultra-high field magnetic resonance imaging (UHFMRI) is set to enhance resolution and diagnostic precision compared to traditional MRI techniques. Recent breakthroughs in nanoparticles (NPs) as sophisticated probes have significantly facilitated the early detection of MASLD [41]. Multifunctional probes featuring two or more distinct imaging modalities have been created for the efficient imaging of liver fibrosis, such as iron oxide/dysprosium oxide NPs (IO-DyO NPs) with a diminutive size of 4 nm [42]. Additionally, the gadolinium-based NaGdF4@PEG@HA nanoprobe exhibited heightened T1 signals in fibrotic livers compared to healthy ones [43]. Improving the accuracy of liver fibrosis prediction in MASLD can be achieved by combining imaging methods with serum fibrosis biomarkers [44, 45]. The inclusion of only Caucasian people and the absence of any external validation are this algorithm's main flaws [45]. The fibrosis 4, NFS, and Hepamet scores are currently the most accurate, well-validated, and straightforward non-invasive tests for ruling out advanced fibrosis. The most validated imaging method available today is VCTE (fibroscan), which, when combined with serum biomarker testing, may help identify MASLD patients who need a liver biopsy to more precisely stage the severity of fibrosis [46].

Fibroscan probes

Adult fibroscan systems come with two different kinds of probes: M probe is utilized for most patients, while an XL probe is for patients who are obese. It is worth noting that the probes provided inconsistent measurements of each LSM and CAP [22]. Compared to the M probe's 25–65 mm depth range, the XL probe's measurement range is 35–75 mm [19]. The M probe's transducer is 7 mm in diameter, yet the XL probe's is 10 mm. The M probe's ultrasonic wave center frequency is 3.5 MHz, while the XL probe's is 2.5 MHz. The XL probe should be used for patients with skin to liver capsule distance (SCD) greater than 25 mm. For both probes, the LSM's shear wave frequency is 50 MHz [47]. In the same population, the LSM derived using the M probe is typically greater than the LSM gained using the XL probe [21–23, 48–50]. LSMs measured with the XL probe were 1.7 ± 2.3 kPa lower than those obtained with the M probe, according to Yang et al. [51]. According to a previous study, the median difference between the LSM readings was 1.4 kPa, while the average difference was 2.3 kPa [50]. According to a third investigation, the XL and M probes' LSM values varied by a median of 2.6 kPa [48]. There was no discernible difference in the AUROCs between the two probes when Oeda et al. [23] applied the probe-specific cutoff values for the CAP and LSM that they had recently published.

The fibroscan test with the XL transducer has been shown to have proven validity and lower test failure rates (1.1% vs. 16%) when compared to the standard transducer because it is calibrated for patients with obesity and morbid obesity [50, 52]. Numerous reports [51, 53–56] attest to the XL transducer's safety and dependability in both pre- and post-operative settings with high success rates.

Fibroscan measurement of fibrosis degree

The degree of liver fibrosis in the LSM is determined by the median value, which is derived solely from a minimum of ten reliable measurements. The interquartile range to the median ratio (IQR/Med) has an impact on the reliability of the LSM results in patients with ten valid LSMs [57, 58]. Generally speaking, the LSM reliability is poor over the 0.3 IQR/Med cutoff point. If the median value is low, it is typical for the IQR/Med to be higher than 0.3 in medical practice; in these situations, the LSM is deemed inappropriate. Consequently, evaluating reliability in terms of LSM values is crucial. Ranges for IQR/Med and Med were created by Boursier et al. [58] in order to assess the test's reliability: while IQR/Med > 0.1 and ≤ 0.3 with any Med value or > 0.3 with Med < 7.1 kPa is seen as dependable, IQR/Med > 0.3 with Med ≥ 7.1 kPa is regarded as unreliable. IQR/Med ≤ 0.1 with any Med value is regarded as very reliable. When the BMI is greater than 30 kg/m^2, 1.204 × LSMXL (LSM using XL probe) + 0.931 is used. The AUROCs with the two probes do not differ considerably, according to reports that use these cutoff values [23, 24].

Factors affecting the LSM

Many patient-related factors have been demonstrated to affect LSM by TE [59, 60]. These include alcohol consumption, right-sided heart failure, hepatic steatosis, elevated bilirubin, biliary obstruction, acute liver failure, obesity, infiltration disorders (like amyloidosis), and a greater distance between the skin and liver capsule. Therefore, when interpreting LSM in these situations, caution should be used. However, factors other than BMI can also impact the LSM in obese patients. The accuracy of LSM results in obese patients is more affected by SCD than by BMI [61]. The diagnostic performance of fibroscan in identifying patients with fibrosis stage ≥ 2 was deemed adequate by Ali et al. [30]. They proposed that, in order to provide a more precise risk assessment for this patient population, higher-than-average LSM cutoff values are likely desirable. Food consumption also results in elevated LSM values, so, fibroscan is recommended to be performed at least a few hours after a meal or after an overnight fast [62–64]. It is advised that a 120-minute fast be followed before an examination [62]. According to Mueller et al. [65], a 1 mg/dL increase in bilirubin results in a 1 kPa increase in LSM, a 2 cm increase in hepatic venous pressure causes a 1 kPa increase in LSM, and LSM rises by 4 kPa for every 100 U/L increase in AST.

The small sample size, high heterogeneity, differences in the study population, research designs, the extent of subcutaneous fat, in addition to the limited number of patients with significant to advanced fibrosis are characteristics of patients with severe or morbid obesity (BMI ≥ 35.0 kg/m^2) may also explain the differences in optimal LSM cutoff values in different studies [66].

Fibroscan in morbidly obese patients

Fibroscan was once believed to be problematic among individuals who are severely obese, with inconsistent results or scan failure occurring in up to 50% of cases [50, 53]. The accumulation of subcutaneous fat on the right chest wall increases the distance between the skin and the liver capsule (SCD), which is almost always the reason for fibroscan failure [50, 67]. Data concerning severe obesity is limited, especially regarding the XL probe's accuracy and appropriateness [68–71]. Employing the fibroscan XL probe alongside a proficient operator, an impressive success rate of 88% was achieved at baseline pre-operative assessments and 100% during follow-up. Various recent studies have utilized the XL probe, reporting comparable high success rates [54, 55]. However, this remains below the figures observed by Naveau et al. [52] and Garg et al. [56].

Disparities between the fibroscan results and the clinical, laboratory, and other imaging modalities are frequently observed in these patients. There is a need to adjust the LSM values for factors affecting their measurement values. This indicates the proportion of false-positive results pertaining to the severity of liver fibrosis in that patient population. This is consistent with additional reports [25, 72]. Ali et al. [30] reported 29.1% (43/148) of their patients with morbid obesity had false positive LSM values using the cutoff of 12.8 kPa for $F \geq 2$. Applying Castéra et al. [73] cutoff value of 7.1 kPa for the same patients will definitely increase the false positive readings.

False positive cases and the need for new cutoff values

Research focusing solely on individuals suffering from severe or morbid obesity (BMI ≥ 35.0 kg/m^2) is limited, characterized by considerable diversity, small participant numbers, and only a few patients exhibiting significant to advanced fibrosis. The use of low cutoff values among individuals with morbid obesity may indeed diminish the diagnostic accuracy of LSM and result in an underappreciation of liver fibrosis [74]. The presence of fatty liver can itself create scattering artifacts, thereby impairing the accuracy of LSM [75]. This could be a contributing factor to the diminished diagnostic precision in obese patients, who typically have a greater degree of steatosis [76]. Eilenberg et al. [77] noted in 2021 a higher proportion of unreliable findings in individuals with a median BMI of 44.4 kg/m^2. However, not only was viability drastically changed, but VCTE diagnostic accuracy was also severely impacted, particularly in patients with BMIs above the median. In contrast to the reported cutoff range of 7.6 to 12.5 kPa for the detection of advanced fibrosis, a significantly higher cutoff of 14.1 kPa had been reported in patients with a BMI ≥ 44.4 kg/m^2. Therefore, additional research is needed to better define LSM cutoff values or cutoff ranges for significant to advanced fibrosis in patients with severe to morbid obesity and MASLD [74, 78, 79].

Patients with severe or morbid obesity (BMI ≥ 35.0 kg/m^2) have a small sample size, high heterogeneity, young ages, and a small number of patients with significant to advanced fibrosis. These factors are what cause the inconsistency of the fibroscan studies. One crucial prerequisite is to design a prospective multicenter study that eliminates any potential selection bias. Every ethnicity must be represented in different regions, both sexes with varying age groups must be equally represented, and only the XL probe should be used. Clinical, laboratory, elastography, and histology data should all be gathered on the same day of surgery. It is necessary to blind pathologists to the patient's data and employ a variety of validation models. It is vital to recruit patients from both Hepatology and obesity clinics to avoid bias in liver enzymes values.

Conclusions

In a subset of patients with morbid obesity (BMI ≥ 40 kg/m^2), fibroscan is not as reliable in assessing the extent of fibrosis. The variations in the ideal LSM cutoff values across studies can be attributed to a number of factors. An important prerequisite is a prospective multicenter study that eliminates any possible selection bias. It seems that higher cutoff values in morbidly obese patients are more accurate and reduce the quantity of false positive results. Given that patients with significant or advanced fibrosis are more likely to develop end-stage liver disease if treatment is not received, determination of fibrosis degree will be crucial in identifying these patients.

Abbreviations

AUROC: area under the receiver operating characteristic curve

BMI: body mass index

CAP: controlled attenuation parameter

FAST: FibroScan-AST

FibRO-3: fibrosis risk score in the morbidly obese-3

HTN: hypertension

IQR/Med: interquartile range to the median ratio

LSM: liver stiffness measurement

MACE: major adverse cardiovascular events

MASH: metabolic associated steatohepatitis

MASLD: metabolic associated steatotic liver disease

MHO: metabolically healthy obesity

MRE: magnetic resonance elastography

NFS: non-alcoholic fatty liver disease fibrosis score

NPs: nanoparticles

SCD: skin to liver capsule distance

TE: transient elastography

VCTE: vibration-controlled transient elastography

Declarations

Author contributions

MTE: Conceptualization, Data curation, Methodology, Supervision, Visualization, Writing—review & editing. MHH: Conceptualization, Formal analysis, Visualization, Writing—review & editing. AAE: Formal analysis, Visualization, Writing—review & editing. HMAT: Methodology, Manuscript administration, Software, Writing—review & editing. YAA: Software, Validation, Writing—review & editing. GME: Data curation, Supervision, Writing—review & editing. EAT: Methodology, Validation, Writing—review & editing. MDE: Data curation, Supervision, Validation, Writing—review & editing.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

All datasets for this study are included in the manuscript and reference articles.

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