Accuracy of controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) for assessing steatosis and fibrosis in non-alcoholic fatty liver disease: A systematic review and meta-analysis

*Yu-tian Cao,[a,b] Liu-lan Xiang,[a,b] Fang Qi,[a,b] Yu-juan Zhang,[a,b] Yi Chen,[c] and Xi-qiao Zhou [b]**

[a]The first clinical medical college of Nanjing University of Chinese Medicine, Nanjing, China
[b]Department of Endocrinology, Affiliated Hospital of Nanjing University of Chinese Medicine, Jiangsu Province Hospital of Chinese Medicine, Nanjing, China
[c]Department of Gastroenterology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

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Summary

Background Non-alcoholic fatty liver disease (NAFLD) is a common chronic liver disease, and among the non-invasive tests, controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) have shown better diagnostic performance in NAFLD. This meta-analysis aimed to evaluate the performance of CAP and LSM for assessing steatosis and fibrosis in NAFLD.

Methods We searched the PubMed, Web of Science, Cochrane Library, and Embase databases for relevant articles published up to February 13th, 2022, and selected studies that met the inclusion and exclusion criteria, and evaluated the quality of evidence. Then we pooled sensitivity (SE), specificity (SP), and area under receiver operating characteristic (AUROC) curves. A random effect model was applied regardless of heterogeneity. Meta-regression analysis and subgroup analysis were performed to explore heterogeneity, and Fagan plot analysis was used to evaluate clinical utility. This meta-analysis was completed in Nanjing, Jiangsu and registered on PROSPERO (CRD42022309965).

Findings A total of 10537 patients from 61 studies were included in our meta-analysis. The AUROC of CAP were 0·924, 0·794 and 0·778 for steatosis grades ≥ S1, ≥ S2 and = S3, respectively, and the AUROC of LSM for detecting fibrosis stages ≥ F1, ≥ F2, ≥ F3, and = F4 were 0·851, 0·830, 0·897 and 0·925, respectively. Subgroup analysis revealed that BMI ≥ 30 kg/m² had lower accuracy for diagnosing S ≥ S1, ≥ S2 than BMI<30 kg/m². For the mean cut-off values, significant differences were found in CAP values among different body mass index (BMI) populations and LSM values among different regions. For diagnosing S ≥ S1, ≥ S2 and = S3, the mean CAP cut-off values for BMI ≥ 30 kg/m² were 30·7, 28·2, and 27·9 dB/m higher than for BMI < 30 kg/m² (P = 0·001, 0·001 and 0·018, respectively). For diagnosing F ≥ F2 and = F4, the mean cut-off values of Europe and America were 0·96 and 2·03 kPa higher than Asia (P = 0·027, P = 0·034), respectively. In addition, the results did not change significantly after sensitivity analysis and the trim and fill method to correct for publication bias, proving that the conclusions are robust.

Interpretation The good performance of CAP and LSM for the diagnosis of mild steatosis (S ≥ S1), advanced liver fibrosis (F ≥ F3), and cirrhosis (F = F4) can be used to screen for NAFLD in high-risk populations. Of note, the accuracy of CAP for the detection of steatosis in patients with obesity is reduced and requires specific diagnostic values. For LSM, the same diagnostic values can be used when the appropriate probes are selected based on BMI and the automated probe selection tool. The performance of CAP and LSM in assessing steatosis in patients with obesity, moderate to severe steatosis, and low-grade fibrosis should be further validated and improved in the future.

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*Corresponding author at: Department of Endocrinology, Affiliated Hospital of Nanjing University of Chinese Medicine, Jiangsu Province Hospital of Chinese Medicine, Nanjing 210029, China.
E-mail address: Zhouxiqiao@njmu.edu.cn (X.-q. Zhou).

Keywords: Controlled attenuation parameter (CAP); Liver stiffness measurement (LSM); Diagnostic accuracy; Non-alcoholic fatty liver disease (NAFLD); Non-alcoholic steatohepatitis (NASH); Meta-analysis

Research in context

Evidence before this study

In recent years, research has found that among the non-invasive tests, controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) using Fibroscan® equipment exhibited high accuracy in quantifying steatosis and fibrosis in patients with NAFLD. However, although CAP and LSM have been used to evaluate steatosis and fibrosis in many studies, the results were inconsistent, especially for the population with obesity and different probes. Detailed pooled estimates of the accuracy of CAP and LSM for assessing steatosis and fibrosis in NAFLD are needed. We searched the PubMed, Web of Science, Cochrane Library, and Embase databases for relevant articles published up to February 13th 2022. Then we pooled diagnostic indexes to analyze the diagnostic accuracy of CAP and LSM and calculated mean cut-offs. Meta-regression analysis and subgroup analysis were performed to explore heterogeneity according to the cut-off value, BMI, probe type, and region, and Fagan plot analysis was used to evaluate clinical utility.

Added value of this study

According to our meta-analysis results, overall, the diagnostic performance of CAP decreased with the severity of steatosis while the diagnostic performance of LSM increased with the aggravation of fibrosis. Subgroup analysis showed that CAP was less accurate in patients with obesity, the mean CAP cut-off values for BMI $\geq$ 30 kg/m^2 were significantly higher than for BMI $<$ 30 kg/m^2. However, for LSM, the accuracy was similar between different subgroups. The lower LSM values obtained with the XL probe in patients with obesity were partially offset by the higher LSM values generated in patients with obesity, resulting in an insignificant difference in LSM values.

Implications of all the available evidence

Considering the good performance of CAP and LSM for the diagnosis of mild steatosis (S $\geq$ S1), advanced liver fibrosis (F $\geq$ F3), and cirrhosis (F = F4), they can be used to screen for NAFLD in high-risk populations. For the population with obesity, higher CAP diagnostic values and more accurate tools for non-invasive detection of steatosis are needed, while the same LSM diagnostic values can be used for patients with obesity when selecting the appropriate probe based on BMI and the automated probe selection tool. The performance of Fibroscan in detecting steatosis in patients with obesity, moderate to severe steatosis, and low-grade fibrosis needs to be further explored and improved.

Introduction

With the prevalence of obesity and type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD) has become the largest chronic liver disease in developed countries,[1] and in the general population, the estimated prevalence of NAFLD is 25·24%.[2] Nonalcoholic steatohepatitis (NASH) is the inflammatory subtype of NAFLD. With time, NASH can progress to cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease.[1,3] Besides, growing evidence shows that NAFLD is a multisystem disease, affecting extra-hepatic organs and regulatory pathways, with an increasing risk of T2DM, cardiovascular (CVD), and chronic kidney disease (CKD).[4] Therefore, it is necessary for the early diagnosis of NAFLD and to take steps to prevent its progression.

So far, liver biopsy is still regarded as the gold standard for NAFLD diagnosis.[1] However, it is limited by invasiveness, cost, sampling error,[5] and procedure-related complications.[6] Thus, there is an urgent need to develop reliable tools for noninvasive diagnosis of NAFLD/NASH.

In recent years, the use of transient elastography (TE) with Fibroscan® equipment (Echosens, Paris, France) to obtain controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) has been seen as a promising tool for noninvasive quantifying hepatic steatosis and fibrosis, respectively,[7,8] and showed low failure (3·2%), high reliability (> 95%) rates, and high reproducibility.[9] Besides, the development of the XL probe for patients with obesity has solved the limitations of the clinical application of CAP and LSM.[10–12] Studies found unreliable measurements were independently associated with body mass index (BMI) $\geq$ 30 kg/m^2, while 83% of patients (BMI $\geq$ 30 kg/m^2) who could not be measured with the M probe could be measured with the XL probe.[10] In patients with obesity, due to thicker subcutaneous fat, the skin-liver capsule distance (SCD) is more than 25 mm, and the XL probe can increase the detection depth (35-75 mm vs M: 25-65 mm) to improve the measurement success rate.

In addition, the new version of the FibroScan equipment includes an automatic probe selection tool that measures SCD and suggests which probe to use (M: SCD < 25 mm, XL: SCD ≥ 25 mm). In clinical practice, physicians can select probes based on BMI and the automated probe selection tool.[13] However, as the use of CAP and LSM became more popular, results began to diverge, particularly regarding differences in diagnostic accuracy and cut-off values between different BMI populations and between different probes. Earlier, several meta-analyses had discussed the accuracy of CAP or LSM alone in NAFLD patients,[14,15] but few studies were included, with only nine studies, which might lead to relatively limited conclusions.

Hence, we did this meta-analysis with the aim of comprehensively evaluating the performance of CAP and LSM for assessing steatosis and fibrosis in NAFLD/NASH.

Methods

Search strategy and selection criteria

This meta-analysis was conducted following the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines.[16] The protocol for this meta-analysis was registered with PROSPERO (CRD42022309965) https://www.crd.york.ac.uk/PROSPERO/#recordDetails.

We searched the PubMed, Web of Science, Cochrane Library, and Embase databases for relevant articles published up to February 13th, 2022. Our search strategy consisted of MeSH terms and entry terms with no restrictions on the language of the articles. We also scanned the reference lists of eligible articles for additional eligible articles that were not retrieved during the literature search.

For example, in PubMed, we searched ("Non-alcoholic Fatty Liver Disease" OR "nonalcoholic fatty liver disease" OR "fatty liver" OR "nonalcoholic fatty liver disease*" OR "fatty liver*" OR "NAFLD" OR "nonalcoholic steatohepatiti*" OR "NASH" OR "steatohepatiti*" OR "liver steatos*" AND "transient elastography" OR "TE" OR "controlled attenuation parameter" OR "CAP" OR "liver stiffness" OR "LSM" OR "FibroScan" AND "diagnos*" OR "assess*" OR "detect*" OR "qualif*" OR "discriminat*" OR "distin*" OR "different*" OR "predict*"). The details of the search strategy are presented in supplementary materials (Table S1).

The inclusion criteria were as follows: (1) Patients: adult NAFLD/NASH patients; (2) Reference standards: liver biopsy was used as the gold standard for the diagnosis of NAFLD/NASH; (3) Index test: steatosis and fibrosis were assessed by using CAP and LSM of Fibroscan® equipment (Echosens, Paris, France); (4) Steatosis and fibrosis staging: steatosis was staged according to the NASH Clinical Research Network scoring system.[17] Fibrosis was staged from F0 to F4 according to the Kleiner score.[17] If fibrosis was assessed according to other scoring systems, data were transformed according to Goodman's method[18] to unify results on the liver fibrosis staging; (5) Studies that provided sensitivity (SE), specificity (SP), sample size or enough information to get true positive (TP), false positive (FP), true negative (TN) and false negative (FN); (6) Studies included at least 20 patients to obtain good reliability.

The exclusion criteria were as follows: (1) Animal experiments, review, conference abstracts, case reports and meta-analyses; (2) Patients with morbid obesity: BMI>40 kg/m^2; (3) Full-text or sufficient data could not be extracted.

Studies from the database were managed using EndNote X9 software to remove duplicate articles. The included articles based on inclusion and exclusion criteria were screened by FQ and Y-JZ, who worked independently. Disagreement was discussed with another author (L-LX) and subsequently resolved via consensus.

The quality of eligible articles was independently assessed by two investigators (FQ, Y-JZ) with the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) checklist[19] by Review Manager Version 5.4.1, and any disagreement was resolved by the third investigator (L-LX). The QUADAS-2 checklist included four parts: patient selection, index test, reference standard, and flow and timing. Each signaling question was judged as "yes" or "no" or "unclear". The risk of bias and concern about applicability in each study were judged as "high" or "low", or "unclear". Concern about applicability assessment does not apply in the flow and timing domain.

Extracted research information includes: (1) Background information: first author, publication year, country, study design, sample size, age, sex, BMI, and probe type; (2) Diagnostic parameters: cut-off values, area under the receiver operating characteristic (AUROC) curves, SE, SP, TP, FP, TN, FN. Then we constructed a diagnostic 2*2 contingency table. If the same original article contains multiple groups of available data, it would be divided into multiple independent studies for data extraction. The process was performed independently by FQ and Y-JZ. Any disagreements were resolved by discussion and consensus.

Data analysis

To analyze the diagnostic accuracy of CAP and LSM in patients with NAFLD/NASH, the summary SE, SP, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with their 95% confidence interval (95% CI) and AUROC with standard errors (SE) were calculated based on TP, FP, FN, and TN. Further, we drew forest plots and constructed summary receiver operating characteristic (SROC) curves.

The threshold effect was analyzed by Spearman correlation coefficient. Cochran's Q statistic and I^2 statistic

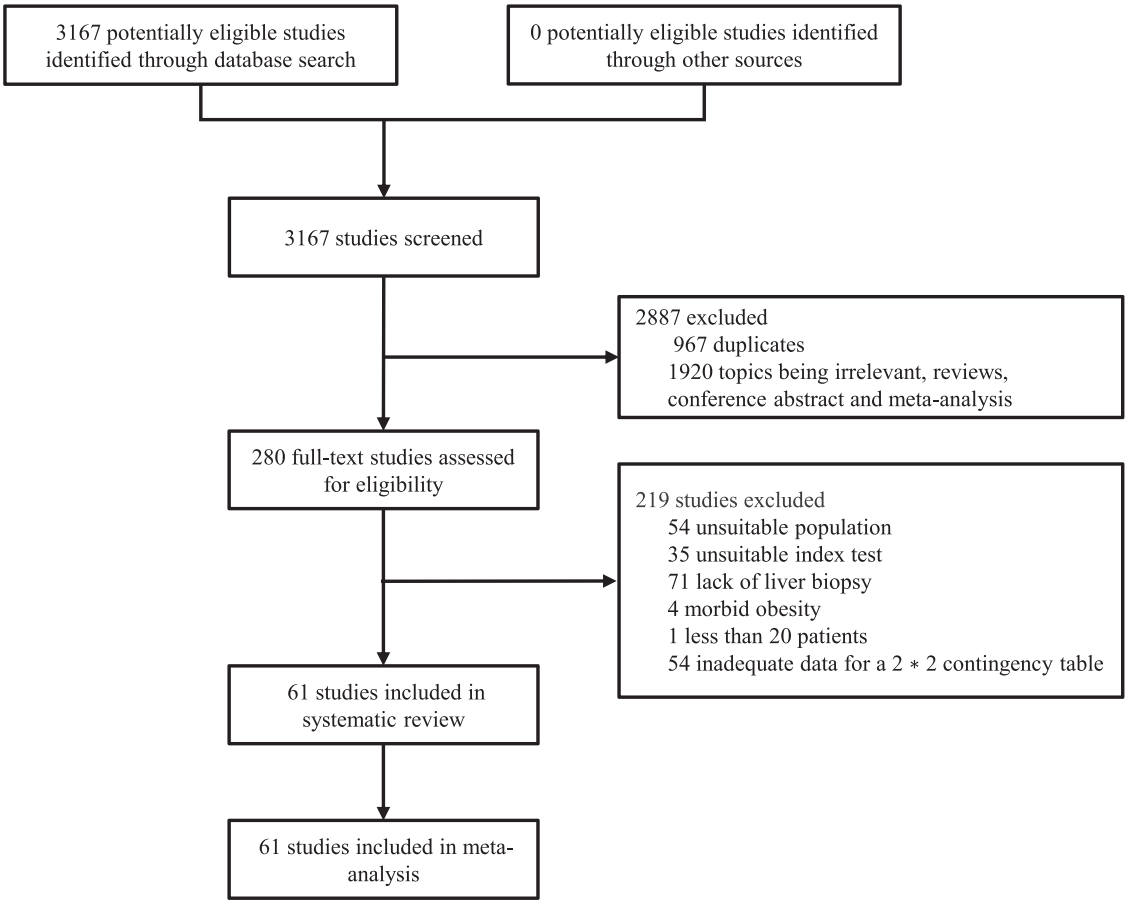

Figure 1. Study selection.

were used to quantitatively evaluate the heterogeneity of studies. When Cochran's Q Statistic showed $P \leq 0{\cdot}10$, it was considered to show significant heterogeneity. Studies with I^2 of 0-25%, 25-75%, and > 75% were considered to have low, moderate, and high heterogeneity, respectively. A random effect model was applied regardless of heterogeneity. Meta-regression analyses were performed to determine the source of heterogeneity. According to the cut-off value, BMI, probe type, and region, we conducted subgroup analyses. The groups were as follows: cut-off value ≥ median value and < median value; BMI < 30 kg/m^2 and ≥ 30 kg/m^2; M and XL probe, Europe and America (EUR-USA) and Asia.

Moreover, according to an estimated prevalence of 25% of NAFLD in the general population, we used Fagan plot analysis to evaluate the pre-test probabilities of 25% and corresponding post-test probabilities in clinical utility. Besides, sensitivity analysis was performed to evaluate the robustness of the results, and Deeks' funnel plot asymmetry test was used to investigate publication bias, and a P value < 0·05 indicated a significant publication bias. The trim and fill method was conducted to rectify the funnel plot asymmetry caused by publication bias.[20] All statistical analyses were done with Meta-Disc Version 1.4 and Stata Version 16.0. The results were considered significant when $P < 0{\cdot}05$.

Role of the funding source

The funding source was used for article processing charges. Beyond that, the funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit it for publication.

Results

Through database searches, 3167 records (PubMed: 1068; EMBASE: 715; Cochrane Library: 501; Web of Science: 1384) were found. After removing duplicates, 2200 records remained, and 1920 records were excluded after browsing titles and abstracts. The remaining 280 records were evaluated in full text, and 219 articles were excluded. Finally, 61 articles were selected for the meta-analysis. The specific screening process is shown in Figure 1.

A total of 10537 patients from 61 articles were included. The characteristics of the 61 included articles are shown in supplementary materials (Table S2). In these articles, 10 articles[21–30] assessed the accuracy of CAP for diagnosing and staging steatosis in NAFLD/NASH, 39 articles[31–69] evaluated the accuracy of LSM for diagnosing and staging fibrosis in NAFLD/NASH, and 12 articles[70–81] evaluated both. Most of the included studies were of good quality. The details are shown in the supplementary materials (Figure S1a and b).

14 studies reported the diagnostic accuracy of CAP for detecting S ≥ S1. The mean cut-off value and range was 268.5 (233·5-304) dB/m. The summary SE and SP of 14 studies were 0·84 (95% CI: 0·83-0·86, Figure S2a) and 0·86 (95%: 0·81-0·90, Figure S2b), respectively. The pooled PLR, NLR and DOR were 4·72 (95%: 3·10-7·17, Figure S2c), 0·16 (95% CI: 0·11-0·22, Figure S2d) and 32·97 (95% CI: 17·40-62·48, Figure S2e), respectively. Finally, the summary AUROC was 0·924 (SE = 0·019, Figure S2f). Similarly, 26 and 25 studies reported the diagnostic accuracy of CAP for detecting S ≥ S2 and = S3 (Figure S3a-f, S4a-f), respectively. For the accuracy of LSM in detecting F ≥ F1, ≥ F2, ≥ F3, and = F4, we pooled 16, 44, 59, and 32 studies, respectively (Figure S5a-f, S6a-f, S7a-f, S8a-f). The detailed summarized diagnostic index data are shown in Table 1, corresponding heterogeneity is shown in Table S4, and the mean cut-off values are shown in Tables 2 and 3.

Meta-regression analyses were performed according to covariates including cut-off value, BMI, probe type, study design, and region. The results showed that BMI (P = 0·0252), cut-off value (P = 0·0313), probe type (P = 0·0304), and region (P = 0·0068) might be the possible sources of heterogeneity (Table S3). Furthermore, we conducted subgroup analyses according to the probe type, BMI, cut-off value, and region. We found that M probe, BMI < 30 kg/m², low cut-off values, and Asia groups showed higher AUROC in detecting S ≥ S1 and ≥ S2, while for diagnosing S = S3, F ≥ F1, F ≥ F2, ≥ F3, and = F4, the AUROC of different probe types, BMI, cut-off values, and regions were similar (Table 1, Figure 2).

Furthermore, we also compared the mean cut-off values between different subgroups. We found that there were significant differences in CAP values among different BMI populations and LSM values among different regions. For diagnosing S ≥ S1, ≥ S2, and = S3, the mean cut-off values of BMI ≥ 30 kg/m² were 30·7, 28·2, and 27·9 dB/m higher than BMI < 30 kg/m² (P = 0·001, 0·001 and 0·018), respectively. For diagnosing F ≥ F2 and = F4, the mean cut-off values of EUR-USA were 0·96 and 2·03 kPa higher than Asia (P = 0·027, P = 0·034), respectively. Interestingly, there were also differences, although not significant, that seemed to follow a pattern: higher mean CAP values for XL probes and EUR-USA groups, and higher mean LSM values for M probes and BMI ≥ 30 kg/m² groups. Specifically, for diagnosing S ≥ S1 and = S3, the mean cut-off values of XL probe were 23·6 and 15·7 dB/m higher than M probe, respectively. For diagnosing S ≥ S1, ≥ S2 and = S3, the mean cut-off values of EUR-USA were 11·2, 16·7, and 6·3 dB/m higher than Asia. Moreover, for diagnosing F ≥ F2, ≥ F3, and = F4, the mean cut-off values of M probe were 0·87, 0·67 and 1·00 kPa higher than XL probe, respectively. For diagnosing F ≥ F1, ≥ F2, and ≥ F3, the mean cut-off values of high BMI were 0·54, 0·72, and 0·09 kPa higher than low BMI, respectively (Tables 2 and 3, Figure 2).

To investigate the clinical utility of CAP and LSM for hepatic steatosis grading and liver fibrosis staging, respectively. We evaluated the pre-test probabilities of 25% and the corresponding post-test probabilities. For diagnosing S ≥ S1, the Fagan plot analysis revealed a PLR and NLR of 11 and 0·09, respectively. A positive CAP value demonstrated a 78% probability of correct diagnosis and a negative CAP value demonstrated a 3% probability of wrong diagnosis (Figure S2g). For diagnosing S ≥ S2 and S = S3, the Fagan plot analysis revealed a PLR and NLR of 2 and 0·26, 2 and 0·36, respectively, and the positive and negative post-test probability were 44% and 8%, 43% and 11%, respectively (Figure S3g, S4g). For diagnosing F ≥ F1, F ≥ F2, F ≥ F3, and F = F4, the Fagan plot analysis revealed a PLR and NLR of 4 and 0·28, 3 and 0·29, 5 and 0·18, 8 and 0·11, respectively, and the positive and negative post-test probability were 55% and 9%, 52% and 9%, 61% and 6%, 72% and 4%, respectively (Figures S5-8g).

In addition, goodness-of-fit and bivariate normality analyses showed that the results were moderately robust to detect steatosis and fibrosis at each stage (Figure S9-15a and b). Furthermore, we used influence analysis and outlier detection to identify relevant outliers (Figure S9-15c and d). After we excluded the relevant outliers, we found no significant changes in the overall results (Table S5), also suggesting that the results are reliable. We used Deeks' funnel plot asymmetry test to assess the publication bias. There was no evidence of publication bias among included studies in diagnosing S ≥ S1 (P = 0·58, Figure S2h), S ≥ S2 (P = 0·09, Figure S3h), F ≥ F1 (P = 0·26, Figure S5h) and F ≥ F3 (P = 0·71, Figure S7h). However, publication bias was found in diagnosing S ≥ S3 (P = 0·00, Figure S4h), F ≥ F2 (P = 0·03, Figure S6h) and F = F4 (P = 0·03, Figure S8h). The results of the trim and fill method showed that for diagnoses S ≥ S3, F ≥ F2, and F = F4, after adding 11, 15, and 12 studies, respectively, there was no significant asymmetry in the filled funnel plots, indicating no publication bias (Figures S4i, S6i and S8i), and no significant changes in the pooled effect values and 95% CI (all P = 0·000), indicating that the results were stable.

Discussion

In this meta-analysis, we found that the AUROC of CAP were 0·924, 0·794 and 0·778 for S ≥ S1, ≥ S2 and = S3,

Category	Subgroup	Case (n)	Sample (n)	SE (95% CI)	SP (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUROC (SE*)
S≥S1		14	2138	0·84 (0·83-0·86)	0·86 (0·81-0·90)	4·72 (3·10-7·17)	0·16 (0·11-0·22)	32·97 (17·40-62·48)	0·924 (0·019)
Probe type	M	6	621	0·92 (0·90-0·94)	0·91 (0·84-0·96)	6·58 (3·08-14·08)	0·09 (0·07-0·13)	84·87 (37·71-191·01)	0·969 (0·011)
	XL	2	176	0·93 (0·89-0·97)	0·89 (0·52-1·00)	5·77 (1·34-24·81)	0·08 (0·04-0·15)	73·55 (11·54-468·99)	/
BMI	< 30	5	564	0·92 (0·90-0·95)	0·91 (0·83-0·96)	6·98 (2·97-16·43)	0·09 (0·06-0·13)	88·20 (35·61-218·50)	0·970 (0·011)
	≥30	9	1574	0·82 (0·80-0·84)	0·82 (0·75-0·88)	3·72 (2·57-5·38)	0·21 (0·15-0·28)	18·64 (11·25-30·89)	0·883 (0·018)
Cut-off value	≥ median	8	1539	0·82 (0·80-0·84)	0·83 (0·75-0·88)	3·91 (2·43-6·31)	0·18 (0·13-0·26)	21·17 (10·86-41·26)	0·887 (0·018)
	<median	6	599	0·90 (0·87-0·92)	0·90 (0·82-0·95)	6·09 (3·00-12·35)	0·12 (0·06-0·25)	59·42 (22·71-155·45)	0·950 (0·022)
Region	Europe and America	7	1242	0·79 (0·76-0·81)	0·80 (0·72-0·86)	3·43 (2·32-5·08)	0·26 (0·21-0·33)	16·63 (10·44-26·28)	0·876 (0·019)
	Asia	7	896	0·92 (0·90-0·94)	0·93 (0·87-0·97)	10·24 (5·42-19·38)	0·10 (0·08-0·12)	119·49 (53·97-264·53)	0·969 (0·010)
S≥S2		26	3414	0·79 (0·78-0·81)	0·64 (0·62-0·67)	2·28 (1·96-2·65)	0·30 (0·26-0·36)	8·61 (6·39-11·59)	0·794 (0·023)
Probe type	M	12	1449	0·82 (0·79-0·85)	0·69 (0·65-0·73)	2·80 (2·09-3·75)	0·24 (0·18-0·32)	13·74 (8·29-22·76)	0·850 (0·031)
	XL	4	357	0·85 (0·80-0·90)	0·52 (0·44-0·59)	1·68 (1·31-2·17)	0·24 (0·11-0·55)	7·22 (3·19-16·31)	0·707 (0·054)
BMI	< 30	12	1260	0·85 (0·82-0·88)	0·65 (0·61-0·69)	2·60 (1·91-3·55)	0·20 (0·13-0·29)	15·29 (8·83-26·49)	0·848 (0·037)
	≥30	14	1978	0·76 (0·74-0·79)	0·64 (0·61-0·67)	2·06 (1·79-2·36)	0·37 (0·32-0·43)	5·83 (4·52-7·52)	0·771 (0·017)
Cut-off value	≥ median	13	2079	0·76 (0·73-0·78)	0·63 (0·60-0·67)	2·03 (1·79-2·29)	0·38 (0·34-0·43)	5·66 (4·64-6·90)	0·770 (0·016)
	<median	13	1135	0·86 (0·84-0·89)	0·66 (0·62-0·70)	2·74 (1·97-3·81)	0·19 (0·13-0·29)	16·75 (9·32-30·11)	0·861 (0·034)
Region	Europe and America	9	1560	0·77 (0·75-0·80)	0·64 (0·60-0·68)	2·21 (1·79-2·73)	0·35 (0·28-0·45)	7·03 (4·47-11·08)	0·743 (0·048)
	Asia	14	1456	0·81 (0·78-0·84)	0·65 (0·61-0·68)	2·37 (1·85-3·04)	0·27 (0·20-0·36)	10·20 (6·35-16·37)	0·822 (0·032)
S=S3		25	3549	0·75 (0·72-0·78)	0·62 (0·60-0·64)	2·18 (1·91-2·49)	0·41 (0·36-0·48)	6·00 (4·50-8·01)	0·778 (0·020)
Probe type	M	13	1773	0·75 (0·71-0·79)	0·63 (0·60-0·65)	2·17 (1·82-2·58)	0·37 (0·28-0·50)	6·89 (4·25-11·16)	0·792 (0·035)
	XL	4	357	0·79 (0·67-0·88)	0·63 (0·57-0·68)	2·10 (1·53-2·90)	0·34 (0·21-0·56)	6·72 (3·41-13·23)	0·817 (0·049)
BMI	< 30	12	1260	0·76 (0·70-0·81)	0·63 (0·60-0·66)	2·13(1·82-2·50)	0·42 (0·32-0·54)	5·71 (3·80-8·58)	0·755 (0·033)
	≥30	12	1965	0·78 (0·74-0·81)	0·62 (0·59-0·64)	2·31 (1·83-2·91)	0·39 (0·33-0·46)	6·87 (4·44-10·64)	0·810 (0·023)
Cut-off value	≥ median	11	1782	0·71 (0·66-0·75)	0·69 (0·67-0·72)	2·62 (2·06-3·33)	0·42 (0·33-0·52)	7·17 (4·31-11·93)	0·797 (0·029)
	<median	14	1767	0·81 (0·77-0·85)	0·55 (0·53-0·58)	1·91 (1·66-2·20)	0·39 (0·32-0·48)	4·84 (3·64-6·44)	0·754 (0·032)
Region	Europe and America	8	1531	0·72 (0·68-0·76)	0·61 (0·58-0·64)	2·24 (1·69-2·97)	0·46 (0·38-0·55)	5·01 (3·20-7·84)	0·767 (0·029)
	Asia	13	1535	0·76 (0·70-0·81)	0·63 (0·60-0·66)	2·02 (1·77-2·30)	0·44 (0·36-0·55)	4·99 (3·62-6·88)	0·744 (0·030)
F≥F1		16	2264	0·73 (0·71-0·75)	0·80 (0·76-0·83)	3·40 (2·74-4·20)	0·29 (0·23-0·36)	12·82 (9·20-17·86)	0·851 (0·016)
Probe type	M	10	1369	0·77 (0·75-0·80)	0·80 (0·76-0·84)	3·67 (3·00-4·48)	0·27 (0·21-0·35)	14·81 (10·84-20·24)	0·863 (0·013)
	XL	1	57	/	/	/	/	/	/
BMI	< 30	10	1384	0·78 (0·75-0·80)	0·79 (0·74-0·83)	3·37 (2·63-4·31)	0·27 (0·21-0·35)	14·09 (9·90-20·04)	0·859 (0·014)
	≥30	6	880	0·66 (0·62-0·70)	0·81 (0·76-0·86)	3·56 (2·29-5·53)	0·32 (0·21-0·49)	11·31 (5·90-21·68)	0·842 (0·039)
Cut-off value	≥ median	9	1661	0·71 (0·68-0·73)	0·83 (0·79-0·86)	4·00 (3·26-4·92)	0·30 (0·23-0·40)	13·67 (10·17-18·38)	0·864 (0·014)
	<median	7	603	0·80 (0·76-0·84)	0·71 (0·64-0·78)	2·66 (1·93-3·66)	0·27 (0·18-0·40)	11·54 (5·51-24·19)	0·831 (0·054)
Region	Europe and America	5	810	0·65 (0·61-0·69)	0·80 (0·74-0·85)	3·28 (1·89-5·70)	0·33 (0·20-0·54)	11·24 (4·73-26·70)	0·844 (0·053)
	Asia	11	1454	0·77 (0·75-0·80)	0·80 (0·75-0·84)	3·60 (2·96-4·38)	0·27 (0·22-0·34)	14·37 (10·62-19·44)	0·860 (0·013)

Table 1 (Continued)

Category	Subgroup	Case (n)	Sample (n)	SE (95% CI)	SP (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUROC (SE*)
F≥F2		44	6186	0·76 (0·75-0·78)	0·73 (0·72-0·75)	3·18 (2·69-3·75)	0·33 (0·29-0·37)	11·06 (8·90-13·74)	0·830 (0·011)
Probe type	M	22	3308	0·77 (0·74-0·79)	0·72 (0·70-0·74)	3·07 (2·47-3·81)	0·32 (0·26-0·38)	11·04 (8·24-14·80)	0·838 (0·015)
	XL	6	647	0·82 (0·77-0·86)	0·66 (0·60-0·71)	2·55 (1·54-4·24)	0·38 (0·30-0·49)	6·48 (4·35-9·66)	0·798 (0·026)
BMI	< 30	21	2787	0·78 (0·76-0·80)	0·73 (0·71-0·75)	3·08 (2·46-3·85)	0·31 (0·26-0·37)	10·96 (8·16-14·71)	0·836 (0·015)
	≥30	20	2894	0·76 (0·74-0·78)	0·74 (0·72-0·77)	3·60 (2·67-4·86)	0·32 (0·27-0·39)	12·51 (8·75-17·89)	0·849 (0·016)
Cut-off value	≥ median	23	3502	0·73 (0·70-0·75)	0·78 (0·76-0·80)	3·57 (2·95-4·32)	0·34 (0·28-0·40)	13·10 (9·39-18·27)	0·854 (0·017)
	<median	19	2544	0·81 (0·79-0·83)	0·66 (0·63-0·68)	2·55 (2·06-3·15)	0·31 (0·26-0·38)	8·70 (6·63-11·41)	0·816 (0·017)
Region	Europe and America	16	2713	0·74 (0·71-0·76)	0·76 (0·73-0·78)	3·25 (2·57-4·11)	0·34 (0·29-0·41)	10·44 (7·59-14·37)	0·832 (0·017)
	Asia	21	2254	0·75 (0·73-0·78)	0·79 (0·76-0·81)	3·58 (2·85-4·50)	0·32 (0·26-0·39)	13·39 (9·17-19·55)	0·854 (0·017)
F≥F3		59	11976	0·83 (0·82-0·84)	0·79 (0·78-0·80)	4·32 (3·78-4·93)	0·21 (0·18-0·25)	22·70 (17·58-29·31)	0·897 (0·010)
Probe type	M	28	5436	0·80 (0·78-0·82)	0·80 (0·79-0·81)	4·55 (3·84-5·39)	0·23 (0·19-0·28)	19·70 (15·30-25·35)	0·886 (0·010)
	XL	5	566	0·70 (0·63-0·77)	0·81 (0·76-0·84)	3·56 (2·49-5·10)	0·31 (0·17-0·54)	13·03 (5·86-28·95)	0·837 (0·025)
BMI	< 30	27	4337	0·81 (0·78-0·83)	0·83 (0·82-0·85)	4·83 (4·27-5·47)	0·24 (0·21-0·28)	21·70 (16·97-27·74)	0·894 (0·008)
	≥30	29	7134	0·84 (0·83-0·86)	0·77 (0·75-0·78)	4·00 (3·28-4·89)	0·17 (0·13-0·23)	27·04 (17·34-42·15)	0·917 (0·017)
Cut-off value	≥ median	25	3417	0·79 (0·76-0·81)	0·84 (0·83-0·86)	5·08 (4·27-6·05)	0·20 (0·15-0·27)	26·72 (18·40-38·81)	0·905 (0·011)
	<median	32	8419	0·84 (0·83-0·85)	0·77 (0·76-0·78)	3·73 (3·16-4·40)	0·22 (0·18-0·26)	19·08 (13·57-26·83)	0·889 (0·015)
Region	Europe and America	27	7629	0·82 (0·81-0·84)	0·78 (0·76-0·79)	4·09 (3·40-4·93)	0·23 (0·18-0·29)	19·27 (13·39-27·73)	0·885 (0·015)
	Asia	22	2616	0·86 (0·83-0·88)	0·83 (0·81-0·84)	4·82 (3·93-5·90)	0·19 (0·16-0·24)	28·08 (19·11-41·25)	0·911 (0·012)
F=F4		32	4594	0·83 (0·79-0·86)	0·85 (0·84-0·86)	6·37 (5·17-7·85)	0·17 (0·12-0·25)	36·63 (25·11-53·45)	0·925 (0·010)
Probe type	M	16	2286	0·82 (0·77-0·86)	0·86 (0·84-0·87)	7·19 (5·13-10·06)	0·17 (0·10-0·29)	31·40 (20·66-47·72)	0·921 (0·012)
	XL	5	566	0·72 (0·60-0·81)	0·87 (0·83-0·90)	6·51 (3·87-10·95)	0·20 (0·06-0·67)	20·79 (10·22-42·27)	0·910 (0·026)
BMI	< 30	17	2178	0·85 (0·80-0·89)	0·88 (0·86-0·89)	7·39 (5·76-9·47)	0·14 (0·07-0·26)	42·55 (27·67-65·44)	0·937 (0·010)
	≥30	13	2235	0·80 (0·75-0·85)	0·82 (0·81-0·84)	5·08 (3·64-7·10)	0·21 (0·12-0·35)	27·07 (14·61-50·18)	0·911 (0·022)
Cut-off value	≥ median	17	2577	0·77 (0·72-0·82)	0·87 (0·86-0·89)	6·83 (5·38-8·68)	0·21 (0·13-0·33)	30·66 (20·34-46·22)	0·925 (0·011)
	<median	14	1929	0·90 (0·85-0·93)	0·83 (0·81-0·85)	5·99 (4·15-8·64)	0·17 (0·11-0·25)	43·82 (21·30-90·12)	0·939 (0·017)
Region	Europe and America	12	2016	0·85 (0·80-0·89)	0·82 (0·80-0·84)	5·24 (3·66-7·52)	0·18 (0·11-0·30)	33·02 (16·87-64·60)	0·925 (0·020)
	Asia	15	1521	0·95 (0·90-0·98)	0·88 (0·86-0·89)	7·72 (5·72-10·43)	0·11 (0·06-0·19)	83·70 (43·88-159·63)	0·959 (0·010)

***Table 1*: Diagnostic accuracy of CAP and LSM in NAFLD/NASH.**

Abbreviations: NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; CAP: controlled attenuation parameter; LSM: liver stiffness measurement; BMI: body mass index; SE: sensitivity; SP: specificity; PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio; AUROC: area under the receiver operating characteristic curve; 95% CI: 95% confidence interval; SE*: standard errors; NA: not applicable.

Category	Subgroup	Case (n)	Sample (n)	Mean Cut-off (range) (dB/m)	D value (dB/m)	*P* value
S≥S1		14	2138	268·5 (233·5-304)		
Probe type	M	6	621	254·4 (233·5-275)	23·6	0·091
	XL	2	176	278·0 (271-285)		
BMI	< 30	5	564	251·2 (233·5-275)	30·7	0·001
	≥30	9	1574	281·9 (261-304)		
Cut-off value	≥ median	8	1539	285·6 (271-304)	34·3	< 0·001
	<median	6	599	251·3 (233·5-266)		
Region	Europe and America	7	1242	274·8 (233·5-304)	11·2	0·313
	Asia	7	896	263·6 (236-285)		
S≥S2		26	3414	288·0 (245-331)		
Probe type	M	12	1449	282·9 (263-313·5)	1·7	0·861
	XL	4	357	281·3 (273-291)		
BMI	< 30	12	1260	272·8 (245-313·5)	28·2	0·001
	≥30	14	1978	301·0 (266-331)		
Cut-off value	≥ median	13	2079	307·4 (289-331)	38·8	< 0·001
	< median	13	1135	268·6 (245-285)		
Region	Europe and America	9	1560	297·6 (245-331)	16·7	0·109
	Asia	14	1456	280·9 (258-331)		
S=S3		25	3549	313·1 (245-366)		
Probe type	M	13	1773	311·6 (267-366)	15·7	0·322
	XL	4	357	327·3 (302-355)		
BMI	< 30	12	1260	298·9 (245-337)	27·9	0·018
	≥30	12	1965	326·8 (267-366)		
Cut-off value	≥ median	11	1782	339·6 (320-366)	47·3	< 0·001
	< median	14	1767	292·3 (245-312)		
Region	Europe and America	8	1531	312·5 (245-345)	6·3	0·629
	Asia	13	1535	306·2 (267-355)		

***Table 2*: Mean cut-off and range of CAP in NAFLD/NASH.**
Abbreviations: NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; CAP: controlled attenuation parameter; BMI: Body Mass Index.

respectively, and the AUROC of LSM for detecting F ≥ F1, ≥ F2, ≥ F3, and = F4 were 0·851, 0·830, 0·897 and 0·925, respectively. From the above data, we could conclude that, overall, the diagnostic performance of CAP decreased with the severity of steatosis, while the diagnostic performance of LSM increased with the aggravation of fibrosis. Fagan plot analysis also showed similar results in clinical utility. This result was also consistent with previous meta-analyses about the diagnostic performance of CAP and LSM in NAFLD/NASH.[14,15] Although ultrasound is the main method for examining NAFLD, it is not sensitive enough to detect steatosis with liver fat content less than 20%,[82] for which CAP has good accuracy. Current EASL and Asia-Pacific guidelines recommend screening for NAFLD in high-risk populations (e.g., obesity, diabetes),[3,83] and CAP is a good option for detecting mild steatosis in this population. In addition, long-term fatty liver may also progress to NASH, liver fibrosis and then advanced liver disease. The good performance of LSM in the diagnosis of advanced liver fibrosis and cirrhosis may be a viable alternative to liver biopsy.

Nevertheless, some studies reported that multiple confounding factors would affect the performance of CAP and LSM, such as fasting conditions,[84,85] probe type,[63] liver transaminases,[42,86,87] extrahepatic cholestasis,[88] waist circumference,[45] and obesity.[42,89] Besides, studies found that steatosis could influence LSM[86,90] and fibrosis could also influence CAP,[91] indicating that LSM and CAP values might influence each other.[79] Our subgroup analyses showed that M probe, low BMI, low cut-off values, and Asia had higher AUROC in detecting S ≥ S1 and ≥ S2, suggesting better diagnostic accuracy. Such results do not seem to be coincidental since Asians have a lower BMI than Europeans and Americans, most of which can be successfully measured with the M probe, and these factors are interlinked and all seem to indicate a higher diagnostic accuracy of CAP in BMI < 30 kg/m² population (Figure 2). Similar conclusion was reached in a previous study: CAP correlated extremely well with actual liver fat percentage in NAFLD patients with BMI < 28 kg/m², especially < 25 kg/m².[91] The reason for the decreased accuracy of CAP in patients with obesity may come from the thicker subcutaneous adipose tissue, so would increasing the probing depth using the XL probe improve accuracy? The results of the subgroup analysis seem to disprove this conjecture. Therefore, it is reasonable to speculate that, in addition

Category	Subgroup	Case (n)	Sample (n)	Mean Cut-off (range) (kPa)	D value (kPa)	*P* value
F≥F1		16	2264	6·67 (5·3-8·6)		
Probe type	M	10	1369	6·63 (5·3-7·5)	/	/
	XL	1	57	/		
BMI	< 30	10	1384	6·47 (5·3-7·5)	0·54	0·242
	≥ 30	6	880	7·01 (5·9-8·6)		
Cut-off value	≥ median	9	1661	7·30 (6·7-8·6)	1·43	< 0·001
	< median	7	603	5·87 (5·3-6·3)		
Region	Europe and America	5	810	6·44 (5·3-8·6)	0·34	0·491
	Asia	11	1454	6·78 (5·9-7·68)		
F≥F2		44	6186	7·61 (5-11)		
Probe type	M	22	3308	7·82 (5-11)	0·87	0·197
	XL	6	647	6·95 (5-8·9)		
BMI	< 30	21	2787	7·62 (5-11)	0·72	0·126
	≥30	20	2894	8·33 (5-11)		
Cut-off value	≥ median	23	3502	8·94 (7·7-11)	2·25	< 0·001
	< median	19	2544	6·70 (5-7·6)		
Region	Europe and America	16	2713	7·66 (6·2-9·8)	0·96	0·027
	Asia	21	2254	8·62 (6·7-11)		
F≥F3		59	11976	9·75 (7·1-13·6)		
Probe type	M	28	5436	9·91 (7·1-13·6)	0·67	0·355
	XL	5	566	9·24 (7·2-11·5)		
BMI	< 30	27	4337	9·54 (7·2-12)	0·09	0·814
	≥30	29	7134	9·63 (6·7-13·6)		
Cut-off value	≥ median	25	3417	10·7 (9·8-13·6)	2·09	< 0·001
	< median	32	8419	8·65 (6·7-9·75)		
Region	Europe and America	27	7629	9·46 (6·7-12·5)	0·49	0·257
	Asia	22	2616	9·95 (7·1-13·6)		
F=F4		32	4594	12·91 (7·9-17·5)		
Probe type	M	16	2286	13·26 (9·5-17·5)	1·00	0·454
	XL	5	566	12·26 (7·9-15)		
BMI	< 30	17	2178	13·12 (7·9-17·5)	0·47	0·645
	≥30	13	2235	12·65 (6·9-16·1)		
Cut-off value	≥ median	17	2577	14·78 (13·1-17·5)	4·34	< 0·001
	< median	14	1929	10·44 (6·9-12·4)		
Region	Europe and America	12	2016	11·94 (6·9-16·1)	2·03	0·034
	Asia	15	1521	13·97 (11-17·5)		

***Table 3*: Mean cut-off and range of LSM in NAFLD/NASH.**
Abbreviations: NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; LSM: liver stiffness measurement; BMI: Body Mass Index; NA: not applicable.

to affecting the measurement by increasing the SCD, excessive subcutaneous fat itself interferes with ultrasound attenuation. In addition, patients with obesity are more likely to have severe steatosis, just as the overall analysis showed that CAP accuracy decreases with increasing steatosis, which increases its diagnostic uncertainty and requires further exploration and improvement in the use of CAP in populations with obesity and severe steatosis. In this case, magnetic resonance imaging-based proton density fat fraction (MRI-PDFF) may be a better option than CAP, which quantifies steatosis more accurately.[92,93] In a meta-analysis, the AUROC for MRI-PDFF diagnosis of S ≥ S1, ≥ S2 and = S3 was 0·97, 0·91 and 0·90, respectively.[92]

Notably, biomarkers are also commonly used non-invasive tests that have shown diagnostic value for fibrosis. A meta-analysis summarized four biomarkers: fibrosis-4 index (FIB-4), NAFLD fibrosis score (NFS), aspartate aminotransferase to platelets ratio index (APRI) and BARD score in the diagnosis of F ≥ F3 with AUROC of 0·84, 0·84, 0·77, and 0·76, respectively.[94] Our analysis showed that the AUROC of LSM for diagnosing F ≥ F3 was 0·897, higher than these biomarkers. However, these biomarkers are cheaper, simpler, and more accessible than LSM due to the limitations of equipment cost and place of use. In primary health care, their use is more advantageous. This is also what the current NAFLD guidelines recommend.[3] However,

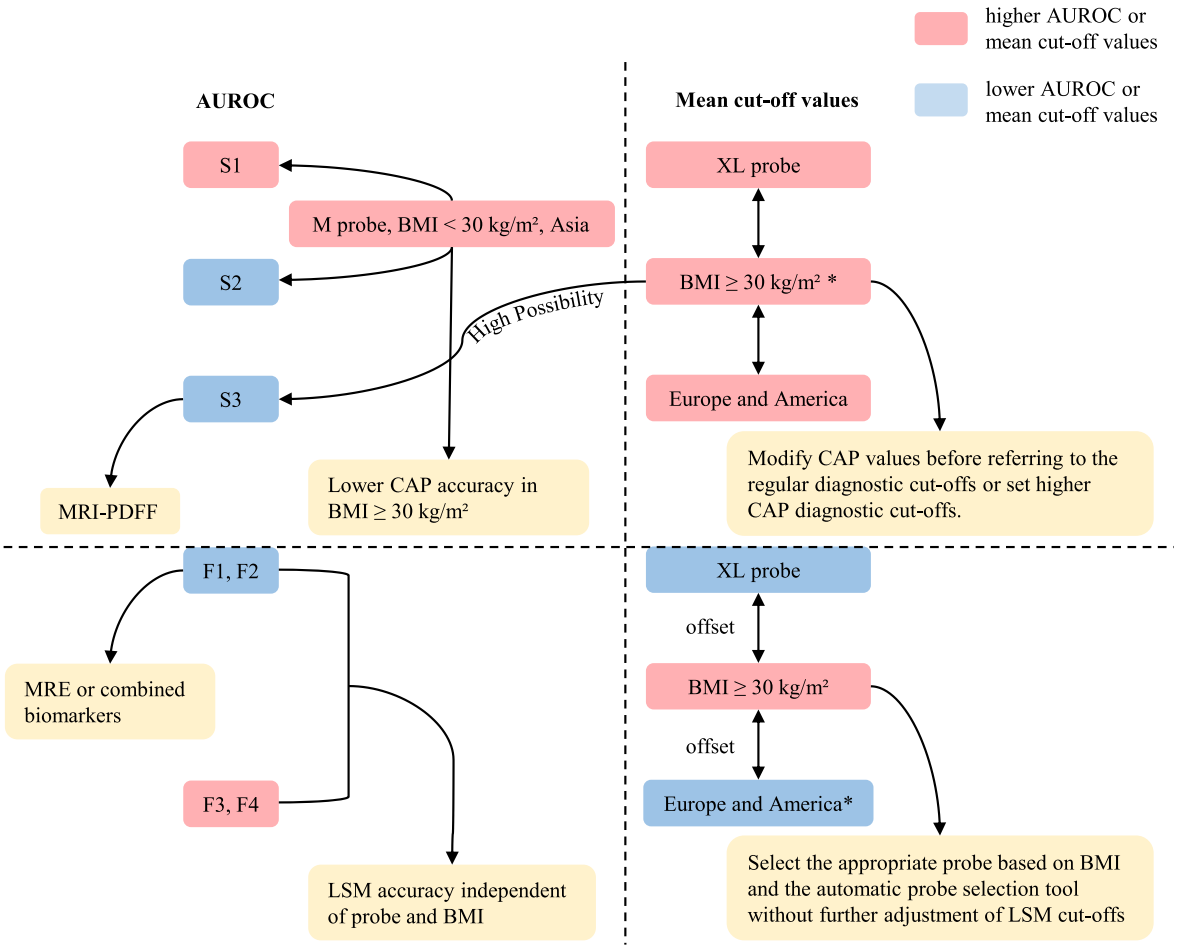

Figure 2. Diagnostic performance of CAP and LSM, mean cut-off values, and influencing factors.

for people at high risk of cirrhosis, such as NAFLD, we recommend choosing LSM with higher accuracy. More importantly, our subgroup analysis showed that the accuracy was similar between different BMI, different probes, and different regions. In addition, some studies have shown that combining LSM with FIB-4 or NFS can improve diagnostic accuracy.[52,56,95] Another FibroMeter vibration-controlled transient elastography (FM-VCTE) model, which combines LSM with biochemical results (platelet count, α2-macroglobulin, urea, prothrombin index, transaminases), also improves the diagnostic accuracy of fibrosis in NAFLD.[36,47] In one study, for the diagnosis of F ≥ F3, the AUROC of LSM was 0·922, while the AUROC of FM-VCTE improved to 0·968.[36] For the diagnosis of F ≥ F1, the combination of LSM with FIB-4 or NFS increased the AUROC of using LSM alone from 0·855 to 0·886 and 0·871, respectively,[56] whereas FM-VCTE increased the positive predictive value for the diagnosis of F ≥ F2,[47] which seems to compensate for the lack of accuracy of LSM in the diagnosis of low-grade fibrosis (F1-2) to a certain extent. However, there are relatively few clinical studies and no relevant meta-analyses, and more studies are needed to verify this. The evidence for the superiority of magnetic resonance elastography (MRE) in the diagnosis of low-grade fibrosis appears to be stronger. For the diagnosis of F ≥ F2, a single study showed an AUROC of 0·91 for MRE, higher than 0·82 for LSM,[93] while a meta-analysis showed an AUROC of 0·91 for MRE, also higher than 0·83 for LSM (Figure 2).[96]

In addition, many studies have also reported that CAP and LSM values might be affected by confounding factors. Hence, we compared the mean cut-off values between different subgroups. We found that there were significant differences in CAP values among different BMI populations. For diagnosing S ≥ S1, ≥ S2 and = S3, the mean CAP cut-off values for BMI ≥ 30 kg/m² were 30·7, 28·2, and 27·9 dB/m higher than for BMI < 30 kg/m², respectively. Interestingly, this had also been confirmed in previous studies. One study found that high BMI was significantly related to an increase in CAP.[97] Another study recalculated the CAP values according to variable BMI, suggesting that when BMI is within 20-25kg/m², for every unit below 25 kg/m²,

4·4 dB/m is added; and when BMI is within 25-30 kg/m², 4·4 dB/m is subtracted for every unit above 25 kg/m².[98] Besides, among different probes and different regions, the CAP values of XL probes and EUR-USA were slightly higher than those of M probes and Asian. Although these differences were not statistically significant, considering the higher prevalence of obesity in the EUR-USA populations and the higher use of the XL probe in the population with obesity, it may exacerbate the overestimation of steatosis in patients with obesity in clinical diagnosis. Therefore, setting higher diagnostic cut-offs for patients with obesity than the routine is needed, but unfortunately, there are no specific diagnostic criteria for this population, or, as mentioned earlier, modifying CAP value for patients with obesity before referring to the regular diagnostic cut-offs (Figure 2).

Moreover, significant differences were found in LSM values among different regions. For diagnosing F ≥ F2 and = F4, the mean cut-off values of EUR-USA were 0·96 and 2·03 kPa higher than Asia, respectively. The mean cut-off values were also slightly higher in Europe-USA than in Asia for diagnoses F ≥ F1 and ≥ F3. This is an interesting finding, and the smaller skeleton and narrower rib space in Asians may be responsible for the higher liver stiffness measurements. There have been a number of studies on the differences in LSM values between different probes, and most agreed that the LSM values obtained using XL probes are lower than those obtained using M probes,[10,62,63,71,77,99] and the guideline summarized that the mean LSM values obtained by XL probes were 1·5 kPa lower than those obtained by M probes (range: 0·8−2·3 kPa).[100] Our analysis results also remained consistent with these studies. As to whether BMI will affect LSM values, the results are not yet uniform. Some believe that it does not,[31,49] and some believe that it does.[41,42,50,51,62,63,77] In our study, the mean cut-off values for BMI ≥ 30 kg/m² were higher than those for BMI < 30 kg/m². However, it is noteworthy that none of the differences between the different probes and BMI populations were statistically significant, indicating that LSM values appear to be independent of probe type and BMI. The XL probe is mostly used in patients with obesity, and its lower LSM values are partially offset by higher LSM values in patients with obesity, which may be the reason for the insignificant difference in LSM values.[62] Therefore, when selecting the appropriate probe according to BMI and the automatic probe selection tool in clinical use, the same LSM diagnostic values can be used without further adjustment (Figure 2).[13,62]

Not long ago, a meta−analysis had investigated the performance of CAP and LSM, but its population involved alcoholic liver disease patients, pediatric patients, and patients with morbid obesity.[101] Studies found that cirrhosis caused by NASH had higher LSM values than cirrhosis caused by chronic hepatitis C,[102] and LSM values should be selected based on different diseases.[35,41] Besides, children and adult NAFLD patients had different histopathological features,[103] and Fibroscan did not accurately predict steatosis or fibrosis in comparison to histology in morbidly patients with obesity.[104] There were also meta-analyses that discussed the accuracy of CAP or LSM alone in NAFLD patients,[14,15] but they included only nine articles, which also led to relatively limited conclusions. Therefore, we included only adult NAFLD/NASH patients, collecting all relevant literature as much as possible. Furthermore, to explore heterogeneity and influence factors, we did meta-regression analysis and subgroup analysis to further analyze the effects of the population with obesity and different probes on CAP and LSM. As we know, this was the first meta-analysis to evaluate the performance of both CAP and LSM for assessing steatosis and fibrosis in adult NAFLD/NASH patients.

Even so, there were some limitations to our work. First, the interval between liver biopsy and index test was unclear or more than 3 months in some included studies, which might increase the risk of bias. Second, partial summary results had great heterogeneity. Although meta-regression analysis and subgroup analysis explained some of the sources of heterogeneity, there were still some that they couldn't explain. Third, due to insufficient data, we could only calculate the mean cut-off values, but could not get the optimal cut-off values. Finally, although we considered the effect of BMI, probe, and region on diagnosis, we were unable to extract sufficient data for other confounding factors such as gender, transaminases, diabetes, and the effect of liver fibrosis on CAP, for further analysis.

In conclusion, the diagnostic performance of CAP decreased with the severity of steatosis while the diagnostic performance of LSM increased with the aggravation of fibrosis. In terms of CAP, its good performance for the diagnosis of mild steatosis can be used to screen for NAFLD in high-risk groups. Note, its low accuracy in patients with obesity and the significant differences in mean cut-off values across different BMI populations suggest the need for special diagnostic values in the population with obesity. All these make its wide application in NAFLD, where the proportion of people with obesity is much higher, a practical problem. In NAFLD, it has high accuracy in diagnosing advanced fibrosis and cirrhosis. Combination with other noninvasive biomarkers seems to improve the diagnosis of F2, and the same diagnostic criteria can be used in the population with obesity when selecting appropriate probes. However, so far, the evidence for noninvasive tests related to NAFLD is still limited, and the future role of CAP and LSM as potential noninvasive alternatives to liver biopsy in the assessment of steatosis and fibrosis should be further validated and improved, especially for the assessment of steatosis in patients with obesity, moderate to severe steatosis, and low-grade fibrosis.

Contributors

Y-TC and X-QZ conceived and designed the study. FQ, Y-JZ and L-LX contributed to data collection. Y-TC, YC and X-QZ conducted the data analysis and interpretation. Y-TC and YC drafted the initial manuscript. X-QZ revised the manuscript. All authors contributed to the article and approved the submitted version.

Data sharing statement

The data analyzed during the current systematic review and meta-analysis is available from the corresponding author on reasonable request.

Declaration of interests

All authors declare no competing interests.

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None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101547.

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