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Original Article

Controlled attenuation parameter for assessment of hepatic steatosis grades: a diagnostic meta-analysis

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Abstract: *Aim*: to evaluate the performance and accuracy of Controlled attenuation parameter CAP for hepatic steatosis detection. *Methods*: PubMed, EBSCO, Elsevier Science, Ovid, and Wiley were selected to search studies until August 31, 2014. Quality Assessment of Diagnostic Accuracy Studies checklist was used to assess the quality of included studies. Heterogeneity was evaluated using Q test. Sensitivity, specificity, diagnostic odds ratio (DOR), and the area under curve (AUC) with its 95% confidence intervals (CIs) were calculated to evaluate the accuracy of CAP for assessment of hepatic steatosis stage (≥ S1, ≥ S2 and ≥ S3). *Results*: Totally 11 studies (13 cohorts) with high methodological qualities were identified. The summary point estimations with 95% CIs of sensitivity, specificity, AUC and DORs were 0.78 (0.71, 0.84), 0.79 (0.70, 0.86), 0.86 (0.82, 0.88), and 14 (7, 27) for ≥ S1; 0.82 (0.74, 0.88), 0.79 (0.73, 0.85), 0.88 (0.85, 0.90) and 18 (10, 30) for ≥ S2; 0.86 (0.82, 0.89), 0.89 (0.86, 0.92), 0.94 (0.91, 0.96) and 51 (35, 76) for ≥ S3. Significant heterogeneity was found among the studies in ≥ S1 and ≥ S3. Threshold effect was existed in ≥ S3, but not in ≥ S1 and ≥ S2. Publication bias was not existed in ≥ S1 and ≥ S2 except ≥ S3. *Conclusion*: CAP provides good sensitivity and specificity for detection of ≥ S1, ≥ S2, and ≥ S3 steatosis. However, future studies with large samples are still necessary to confirm the clinical application.

Keywords: Controlled attenuation parameter, hepatic steatosis, diagnostic meta-analysis

Introduction

Hepatic steatosis is characterized by an accumulation of fat mass > 5% of liver wet weight or > 5% of the hepatocytes containing fatty deposits [1]. Hepatic steatosis is caused by accumulation of triglycerides (TG) in hepatocytes. The other causes for hepatic steatosis include alcohol abuse, viral hepatitis, nutritional administration, medications, and acute fatty liver of pregnancy [2, 3]. The hepatic steatosis can lead to the metabolic dysfunction of liver, which may progress to irreversible liver damage, fibrosis, cirrhosis, and hepatocellular carcinoma [4]. The incidence is increasing especially in countries with high rates of obesity and type 2 diabetes [5, 6]. Therefore, accurate diagnosis of hepatic steatosis *via* detecting its extent plays an important role in evaluating the clinical prognosis.

Although liver biopsy is traditionally used as the gold standard for hepatic steatosis diagnosis, it has several disadvantages which make it not a first-line test. For example, liver biopsy is invasive, has sample variability and low acceptance for patients, and may associate with severe complications [7, 8]. In recent years, efforts have been made to develop some noninvasive methods for hepatic steatosis assessment. Two scoring systems, the Fatty Liver Index and Hepatic Steatosis Index, have been developed, but they were not extensively validated in external data [9, 10].

FibroScan, as the advanced transient elastography device, has been regarded as an optimal technique and has shown positive results for detecting the degree of hepatic steatosis [11]. FibroScan is a noninvasive examination and can distinguish the patients with chronic liver disease away from liver biopsy. It is reported that the results of FibroScan have good repeatability which can used as continuous observation indexes [1]. Based on the ultrasonic properties of the radiofrequency and back prop-

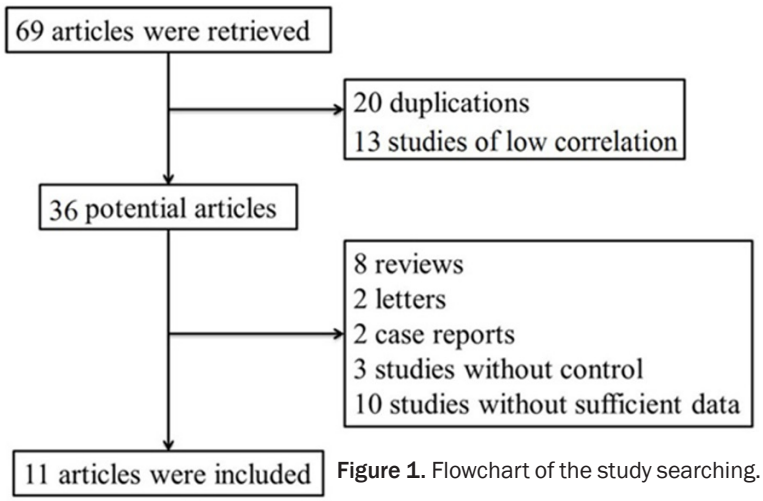

Figure 1. Flowchart of the study searching.

agated signals coupled with the FibroScan, a novel technology, namely controlled attenuation parameter (CAP), was developed to determine the severity of hepatic steatosis. Using Field II simulations, Sasso *et al*. [12] firstly validated CAP as an estimate method of ultrasonic attenuation at 3.5 MHz, and they suggested CAP was an immediate and efficient process to detect and quantify hepatic steatosis. Moreover, Shi and his colleagues [13] had performed a meta-analysis to assess the diagnostic accuracy of CAP. Nine studies with 11 cohorts have been analyzed in the meta-analysis, and they demonstrated that CAP has good sensitivity and specificity for hepatic steatosis detection; however, it is limited in the accuracy of steatosis. In addition, some new studies about CAP detection for hepatic steatosis have been published after this study. Therefore, we conducted a meta-analysis to evaluate the performance and accuracy of CAP for hepatic steatosis detection.

Materials and methods

Data sources and searches

PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), EBSCO (http://search.ebscohost.com/), Elsevier Science (http://www.elsevier.com/), Ovid (http://gateway.ovid.com/), and Wiley (http://onlinelibrary.wiley.com/) were selected to search studies until August 31, 2014. The search terms were "transient elastography" and "liver steatosis", "hepatic steatosis" in combination with "controlled attenuation parameter" or "CAP". References of the eligible articles were also searched.

Inclusion and exclusion criteria

The inclusion criteria were: (1) studies evaluated liver steatosis using CAP; (2) the diagnostic gold standard was liver biopsy; (3) the pathologic category for liver steatosis was classified as stage 0 (S0: < 5% steatosis), stage 1 (≥ S1: 5%-33% steatosis) , stage 2 (≥ S2: 34%-66% steatosis) and stage 3 (≥ S3: > 66% steatosis); (4) the assessment index contained sensitivity, specificity, negative predictive value (NPV), and/or positive predictive value (PPV). (5) the language was restricted to English.

The exclusion criteria were as follows: (1) studies without original data; (2) the subjects of the study were less than 39.

Study selection and data extraction

Two investigators respectively assessed the eligible studies and extracted data from the included articles. Disagreements were settled by discussion with a third investigator. The data comprised of the first authors, county, publication year, the number of cases, age, body mass index (BMI), gender, liver disease, prevalence of ≥ S1, ≥ S2, and ≥ S3, and CAP cut-off values for ≥ S1, ≥ S2, and ≥ S3. Moreover, true positive, false positive, true negative, and false negative were abstracted to calculate sensitivity, specificity, PPV and NPV.

Quality assessment

Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist was used to assess the quality of each study. The checklist has 14 items, and each item is scored as "yes", "no", or "unclear". If the item scored "yes", then received 1 point; if scored "no" or "unclear", then received 0 point. Score > 10 was considered to be high methodological quality.

Data synthesis and statistical analysis

Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (DOR) with its 95% confidence intervals (CIs) were calculated to evaluate the accuracy

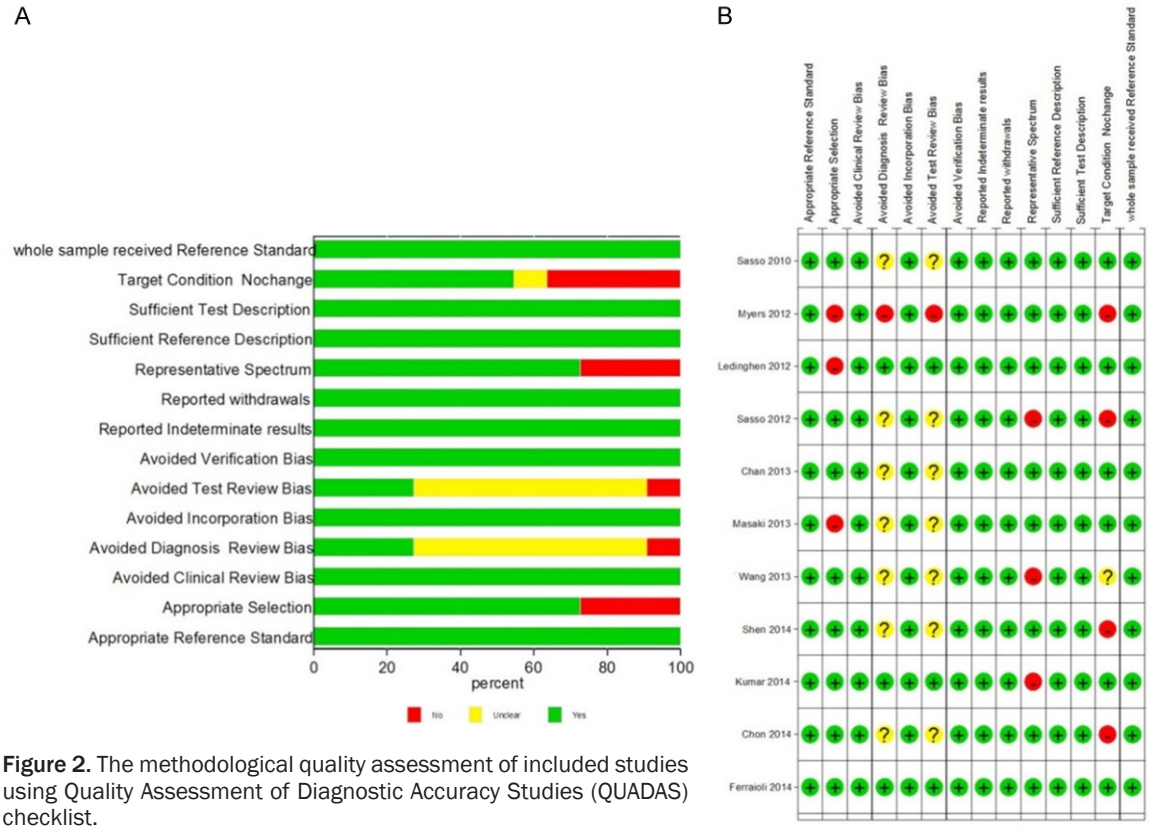

Figure 2. The methodological quality assessment of included studies using Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist.

of CAP. The threshold effect, as the primary cause of heterogeneity in test accuracy studies, was also analyzed with Meta-DiSc [14]. Hierarchical summary receiver operating characteristic (HSROC) curves were plotted, and the area under curve (AUC) with corresponding 95% CI was also counted. Heterogeneity was evaluated using Q test, and $P < 0.05$ represents the presence of heterogeneity. Publication bias was decided using Deek's funnel plot asymmetry test. All statistical analyses were conducted by STATA version 11.0 (StataCorp, College Station, TX, USA), briefly the MIDAS and METANDI commands.

Results

Searching result and study characteristics

The selection flowchart is shown in **Figure 1**. According to the inclusion and exclusion criteria, a total of 69 studies were retrieved. Among them, 20 were duplications and 13 had low correlation. Besides, 8 reviews, 2 letters, 2 case reports, 3 studies without control, and 10 studies without sufficient data were eliminated. Therefore, a total of 11 studies [12, 15-24] were identified in our research. The result of quality assessment suggested that all included studies had high methodological qualities (**Figure 2**).

The extracted characteristics are listed in **Table 1**. A total of 2076 subjects were included in the 11 studies. Particularly, Kumer *et al.* [18] performed 3 cohort studies that contained 146 chronic hepatitis B virus (HBV) infected patients, 108 chronic hepatitis C virus (HCV) infected patients, and 63 non-alcoholic fatty liver disease (NAFLD) patients. Thus, there were 13 cohorts in our study.

The diagnostic accuracy of CAP

CAP accuracy for ≥ S1 was evaluated in 11 studies containing 12 cohorts (**Figure 3**). The CAP cut-off values ranged from 214 to 289 dB/m, and the median was 238 and 250 dB/m (**Table 2**). The summary sensitivity and specificity were 0.78 (95% CI: 0.71, 0.84) and 0.79 (95% CI: 0.70, 0.86) respectively. The positive likelihood ratio was 3.7 (95% CI: 2.5, 5.6) and the negative likelihood ratio was 0.27 (95% CI: 0.19, 0.39). The summary DOR was 14 (95% CI: 7, 27), and the AUC was 0.86 (95% CI: 0.82, 0.88, **Figure 5A**).

Table 1. The extracted characteristics of the included studies

Author	Country	Year	Journal	Liver disease	Case number	The percentage of males (%)	Age	BMI
M Sasso	France	2010	Ultra in Med Bio	CLD 17 ALD 39 NAFLD 17	73	64	49±12	25±4
RP Myers	Canada	2012	Liver Inter	Hepatitis 67 NAFLD 72 Other 14	153	93.7	50 (41-56)	32 (30-34)
VD Ledinghen	France	2012	Liver Inter	NAFLD 28 HCV 40 ALD 6 Other 38	112	48.2	53.8±12.2	25.8±4.2
M Sasso	France	2012	J V Hepato	HCV	615	63.5	47.9±11.6	24.1±3.7
M Kumar	Malaysia	2013	J Gastro Hepato	HBV 146	146	77.4	38 (18-71)	24.3±3.6
				HCV 108	108	56.5	46.5 (18-71)	24.7±3.3
				NAFLD 63	63	86.8	37 (18-66)	25.1±2.0
K Masaki	Japan	2013	Hepato Rea	HBV 17 HCV 58 NASH 40 Other 40	155	59.3	55 (24-91)	24.4 (15.4-39.2)
CY Wang	China Tianjin	2014	W J Gastra	HBV	88	70.4	38.32±12.99	24.16±4.97
Feng Shen	China shanghai	2014	W J Gastra	NAFLD 52 HBV 100	152	69.7	35 (28-49)	24.9 (22.5-27.7)
WK Chan	India	2014	J Gastro Hepato	NAFLD 101 Control 60	161	51.5	50.3±11.3	29.4±3.9
YE Chon	Korea	2014	Liver Inter	CLD 135	135	64.4	51 (18-63)	24.4 (14.3-33.8)
G Ferraioli	Italy	2014	W J Gastra	HBV 82 HCV 28 HIV, HCV 5	115	73.9	43.1±10.5	24.8±4.2

CLD: chronic liver disease; ALD: alcoholic liver disease; NAFLD: non-alcoholic fatty liver disease; HCV: hepatitis C virus; HBV: hepatitis B virus; NASH: nonalcoholic steatohepatitis; HIV: Human Immunodeficiency Virus; BMI: body mass index.

CAP accuracy for ≥ S2 was evaluated in 10 studies containing 12 cohorts (**Figure 4**). The CAP cut-off values ranged from 230 to 311 dB/m, and the median was 259 and 263 dB/m (**Table 2**). The summary sensitivity and specificity were 0.82 (95% CI: 0.74, 0.88) and 0.79 (95% CI: 0.73, 0.85) respectively. The positive likelihood ratio was 4.0 (95% CI: 3.0, 5.3) and the negative likelihood ratio was 0.22 (95% CI: 0.15, 0.33). The summary DOR was 18 (95% CI: 10, 30), and the AUC was 0.88 (95% CI: 0.85, 0.90, **Figure 5B**).

Forest plots of sensitivity and specificity of CAP accuracy for ≥ S3 was not drawn because of the limited data. The results are shown in **Tables 2** and **3**. The CAP cut-off values ranged from 266 to 327 dB/m, and the median was 290 dB/m. The summary sensitivity was 0.86 (95% CI: 0.82, 0.89) and specificity was 0.89 (95% CI: 0.86, 0.92). The positive likelihood ratio was 8.1 (95% CI: 6.3, 10.4) and the negative likelihood ratio was 0.16 (95% CI: 0.12, 0.20). The summary DOR was 51 (95% CI: 35, 76), and the AUC was 0.94 (95% CI: 0.91, 0.96).

Heterogeneity examination, threshold effect, and publication bias

Significant heterogeneity was found among the studies involved in ≥ S1 (Q = 5.732, $P = 0.028$) and ≥ S3 (Q = 49.5, $P < 0.0001$). Threshold effect was existed among studies involved in ≥ S3 ($P < 0.03$), but not in ≥ S1 ($P = 0.09$) or ≥ S2 ($P = 1$). Moreover, basing on the Deek's funnel plot asymmetry test, publication bias was not existed among the included studies in ≥ S1 ($t = -0.12$, $P = 0.91$) and ≥ S2 ($t = 1.75$, $P = 0.216$) except for ≥ S3 ($t = 1.75$, $P = 0.093$). The results are presented in **Table 4**.

Discussion

CAP has been performed to evaluate the grades of hepatic steatosis in different population with various causes. In the present study, a total of

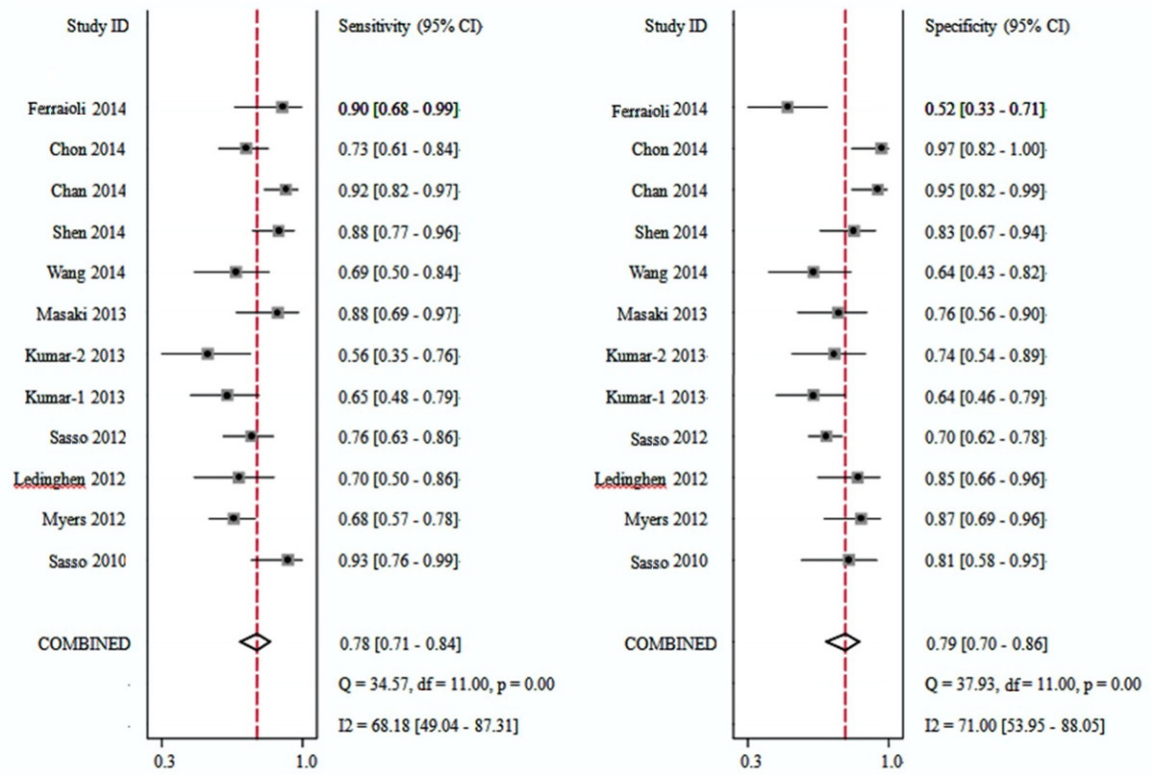

Figure 3. Forest plots of sensitivity and specificity of controlled attenuation parameter (CAP) for the detection of stage 1 (S1) hepatic steatosis.

11 studies with 13 cohorts were included. According to the results, CAP had good sensitivity, specificity, and high AUC for detection of ≥ S1, ≥ S2, and ≥ S3 steatosis that were diagnosed by liver biopsy.

Several non-invasive methods including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and hydrogen (1H) MRI have been used in detection of hepatic steatosis, but some limitations still exist [25, 26]. Ultrasound is accepted for screening of fatty liver because it is inexpensive and it has an acceptable sensitivity and specificity, but it cannot reliably quantify fat accumulation and distinguish fibrosis from steatosis [27]. Non-enhanced CT has been suggested to quantify > 30% histologic grade of hepatic steatosis with 100% specificity and 82% sensitivity [28]. However, the CT values were demonstrated to be significantly varied with different manufactures' multi-detector row CT or different generations of CT scanners [29]. Besides, the radiation exposure should be also taken into consideration especially for longitudinal studies and for children. 1H MRI is conducted in the molecular level *in vivo*. Both and colleagues [25] demonstrated that the mean sensitivity and specificity range for MRI were 82.0-97.4% and 76.1-95.3%, and for 1H MRI were 72.7-88.5% and 92.0-95.7% respectively. Nevertheless, it should be mentioned that the imaging procedure and the examination result are too complex for fully understanding and that the 1H MRI is not available for all clinical scanners [26].

CAP, as a novel method for detection and quantification of hepatic steatosis has multiple advantages. First, its use is not influenced by liver stiffness and fibrosis, which means CAP can be used to evaluate steatosis and fibrosis at the same time [17]. Second, it is an immediate, objective, inexpensive, and easy performed method to detect and quantify steatosis compared with other assessment modalities. Third, CAP probes a liver volume approximately 100 times larger than liver biopsies, which indicates that the influence by sample error is less for CAP. Consequently, based on these features, CAP will be popularly accepted as a reliable assessment tool for steatosis screening and quantification by radiologists in clinical practice.

Table 2. The performance of CAP in the included studies

Author	≥ S1						≥ S2						≥ S3					
	CAP cut-off	AUC	Se	Sp	PPV	NPV	CAP cut-off	AUC	Se	Sp	PPV	NPV	CAP cut-off	AUC	Se	Sp	PPV	NPV
M Sasso	238	0.91	0.91	0.81	0.87	0.87	259	0.95	0.89	0.86	0.8	0.92	292	0.89	1	0.78	0.28	1
RP Myers	289	0.79	0.68	0.88	0.94	0.49	288	0.76	0.85	0.62	0.55	0.88	283	0.7	0.94	0.47	0.17	0.98
VD Ledinghen	266	0.84	0.69	0.85	0.83	0.73	311	0.86	0.57	0.94	0.81	0.83	318	0.93	0.87	0.91	0.65	0.97
M Sasso	222	0.82	0.76	0.71	0.53	0.87	233	0.86	0.87	0.74	0.33	0.98	290	0.88	0.78	0.93	0.15	1
M Kumar	214	0.683	0.649	0.64	0.667	0.62	255	0.793	0.778	0.8	0.457	0.94	266	0.841	0.75	0.804	0.182	0.982
	224	0.658	0.576	0.73	0.667	0.651	251	0.667	0.583	0.774	0.424	0.867	305	0.916	0.714	0.921	0.385	0.976
	/	/	/	/	/	/	258	0.79	0.784	0.731	0.806	0.704	283	0.763	0.714	0.679	0.022	0.4
K Masaki	280	0.878	0.87	0.77	0.752	0.87	/	/	/	/	/	/	/	/	/	/	/	/
CY Wang	220	0.711	0.694	0.72	0.717	0.633	230	0.868	0.833	0.781	0.893	0.65	284	0.974	1	0.969	1	0.857
Feng Shen	253	0.92	0.888	0.83	0.878	0.839	285	0.92	0.933	0.832	0.7	0.967	310	0.88	0.923	0.791	0.293	0.991
WK Chan	263	0.97	0.918	0.94	0.957	0.881	263	0.86	0.969	0.677	0.67	0.97	281	0.75	1	0.531	0.169	1
Y E Chon	250	0.885	0.731	0.95	0.971	0.615	299	0.894	0.824	0.861	0.667	0.935	327	0.8	0.778	0.841	0.259	0.981
G Ferraioli	219	0.76	0.911	0.52	0.569	0.892	296	0.82	0.6	0.915	0.529	0.935	/	/	/	/	/	/

S1: stage 1; S2: stage 2; S3: stage 3; CAP: controlled attenuation parameter; AUC: area under curve; Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value.

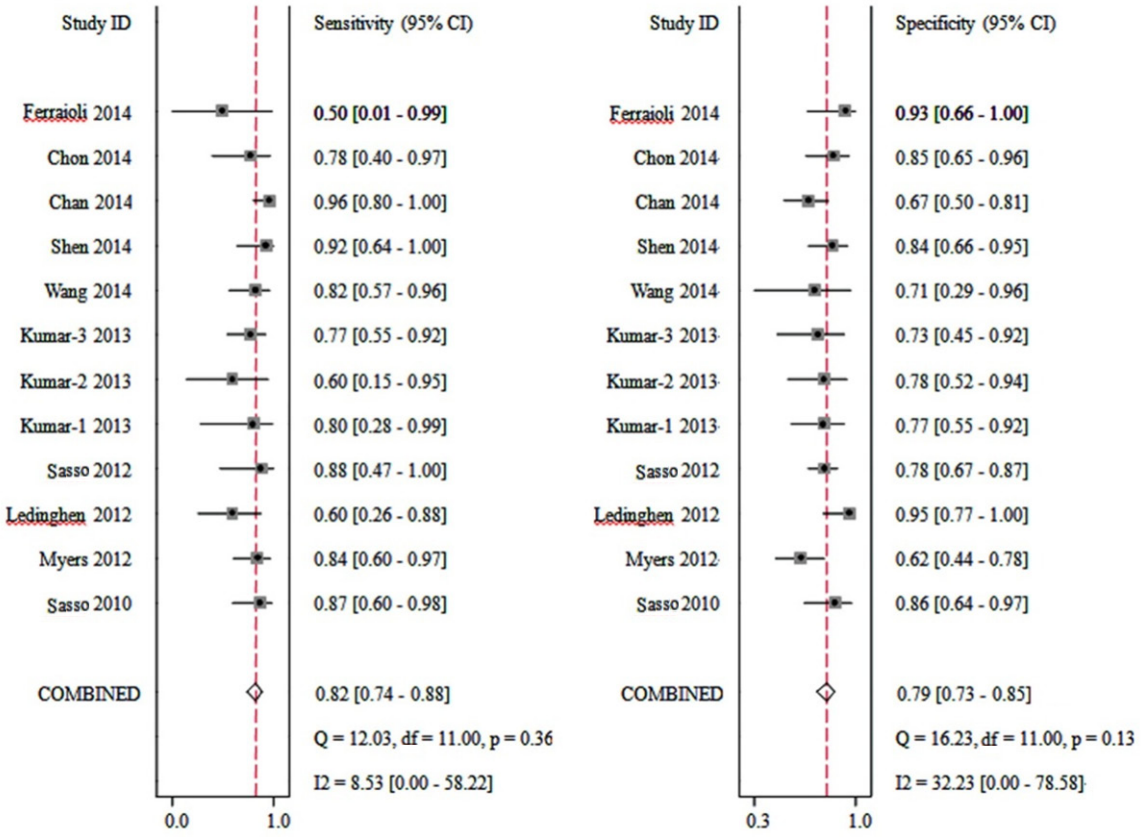

Figure 4. Forest plots of sensitivity and specificity of controlled attenuation parameter (CAP) for the detection of stage 2 (S2) hepatic steatosis.

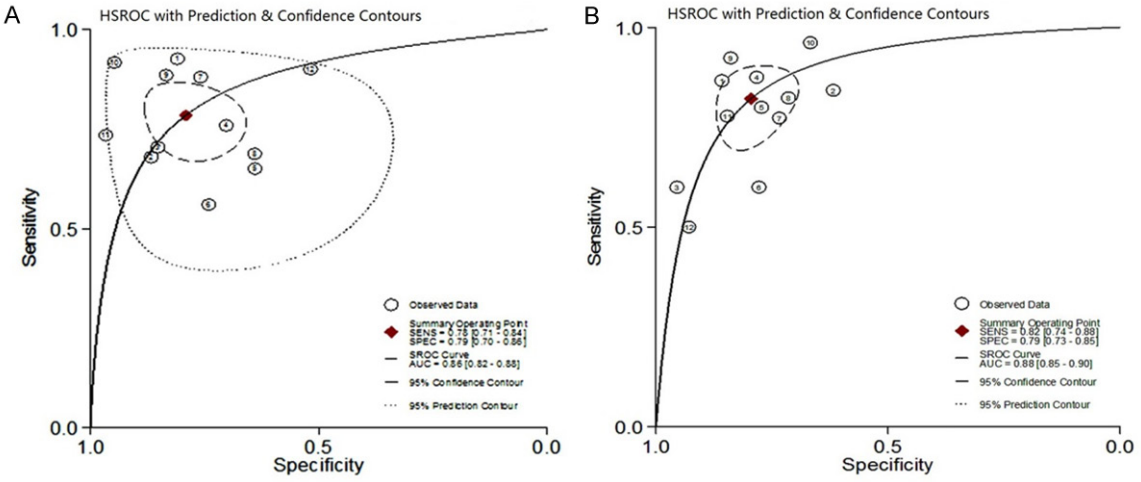

Figure 5. Hierarchical summary receiver operating characteristic (HSROC) curves of controlled attenuation parameter (CAP) for the detection of hepatic steatosis. A. Detection of stage 1 (S1) hepatic steatosis; B. Detection of stage 2 (S2) hepatic steatosis.

A previous meta-analysis was conducted by Shi *et al*. [13]. In their study, a total of 9 studies were analyzed, and the results demonstrated that CAP offered good sensitivity (≥ S1: 0.78, 0.69-0.84; ≥ S2: 0.85, 0.74-0.92; ≥ S3: 0.83, 0.76-0.89) and specificity (≥ S1: 0.79, 0.68-

Table 3. The results of controlled attenuation parameter (CAP) for the detection of stage 1 (≥ S1), stage 2 (≥ S2) and stage 3 (≥ S3) hepatic steatosis

Disease		≥ S1		≥ S2		≥ S3	
		Point estimation	95% confidence intervals	Point estimation	95% confidence intervals	Point estimation	95% confidence intervals
Indexes	Sensitivity	0.78	[0.71, 0.84]	0.82	[0.74, 0.88]	0.86	[0.82, 0.89]
	Specificity	0.79	[0.70, 0.86]	0.79	[0.73, 0.85]	0.89	[0.86, 0.92]
	Positive likelihood ratio	3.7	[2.5, 5.6]	4.0	[3.0, 5.3]	8.1	[6.3, 10.4]
	Negative likelihood ratio	0.27	[0.19, 0.39]	0.22	[0.15, 0.33]	0.16	[0.12, 0.20]
	Diagnostic odds ratio	14	[7, 27]	18	[10, 30]	51	[35, 76]
	AUC	0.86	[0.82-0.88]	0.88	[0.85-0.90]	0.94	[0.91-0.96]

Table 4. Heterogeneity examination, threshold effect, and publication bias

	≥ S1			≥ S2			≥ S3		
	Statistics	*P* value	Result	Statistics	*P* value	Result	Statistics	*P* value	Result
Heterogeneity	Q = 5.732	0.028	Yes	Q = 49.5	3.045	No	Q = 49.5	< 0.0001	Yes
Threshold effect	/	0.09	No	/	1	No	/	< 0.03	Yes
Publication bias	t = -0.12	0.910	No	t = 1.75	0.216	No	t = 1.75	0.093	Yes

0.86; ≥ S2: 0.79, 0.68-0.87; ≥ S3: 0.79, 0.68-0.87), and high HSROC (≥ S1: 0.85, 0.81-0.88; ≥ S2: 0.88, 0.85-0.91; ≥ S3: 0.87, 0.84-0.90). But, they did not retrieve literature published in 2014. In the current meta-analysis, another 5 studies published in 2014 were included and 3 studies in the previous study were excluded. Among the 3 studies, 2 studies respectively performed by Wong *et al*. [30] and Enooku *et al*. [31] only have abstract that cited from conferences and the study performed by Friendrich-Rust *et al*. [32] did not provide sufficient data. According to our results, no significant change was found for specificity, sensitivity, and HSROC compared with the previous study. Nevertheless, the threshold effect was also analyzed in the present study, which demonstrated that the difference in threshold was the primary cause of heterogeneity among the included studies.

In addition, heterogeneity was existed among the included studies. This heterogeneity may be caused by clinical heterogeneity and the existed threshold effect, since the race of studied subjected, the evaluation system of gold standard, and the cut-off value of transient elastography diagnose were different among the included studies. Moreover, bias for steatosis staging detected by FibroScan was found among different studies, as a unified reference for all stages of fibrosis (F0-F4) was not unified worldwide. For example, the cut-off value for obvious fibrosis ranges from 5.8 kpa to 9.3 kpa, and for early liver cirrhosis ranges from 9.4 kpa to 15.4 kpa. Thus, more studies with larger samples are still needed for further validation.

There are some limitations in the present study. Firstly, FibroScan itself has limitations, which may have an influence on the accuracy and clinical application. For example, the accuracy would decrease for female, elder and high BMI patients. Extrahepatic cholestasis, ascites, large blood vessels around liver, and narrow rib space may also influence the detecting and limit the use of FibroScan. In addition, liver stiffness may also correlate with the serum Alanine transaminase (ALT). Secondly, a significant heterogeneity was presented, which may influence the reliability we concluded though the bivariate model has been selected. Lastly, subgroup analyses of different causes were not conducted because of the limited studies and insufficient information.

Conclusion

In conclusion, the present meta-analysis demonstrates that CAP provides good sensitivity and specificity for detection of ≥ S1, ≥ S2, and ≥ S3 steatosis. We speculate that CAP is an efficient method to detect hepatic steatosis severity. However, future studies with large samples are still necessary to confirm or evaluate the clinical application.

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Disclosure of conflict of interest

None.

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