Table 1. Characteristics of Included Studies Assessing the Diagnostic Accuracy of SSM for the Detection of Esophageal Varices in Patients With Chronic Liver Disease

Study	Location	Design	Time period	Technique	Total patients	Unreliable SSM	No. of patients with any EV and significant EV	Cut-off for presence of EV and significant EV	TP	FP	FN	TN
Al-Dahshan[23]	Jeddah, Saudi Arabia	Case-control	NR	TE	60	NR	30 (50%)	50.4 kPa	24	8	6	22
Borghi et al[28] (abstract)	Bologna, Italy	Cross-sectional	NR	ARFI	44[a]	1[a]	Any EV: 24 (54.5%)	3.08 m/s	17	9	7	10
							Significant EV: 10[b]	3.48 m/s	7	7	3	27
Bota et al[24]	Timisoara, Romania	Cross-sectional	2009–2011	ARFI	169[c]	3	Any EV: 101 (59.8%)	3.48 m/s	31	14	70	54
							Significant EV: 62/145[d]	3.55 m/s	61	66	1	17
Calvaruso et al[29] (abstract)	Palermo, Italy	Cross-sectional	2008–2011	TE	104[e]	8	Any EV: 54 (51.9%)	50.0 kPa	35	16	19	26
							Significant EV: 26[d]	54.0 kPa	21	21	5	49
Colecchia et al[5]	Bologna, Italy	Cross-sectional	2009–2011	TE	113[f]	13	53 (46.9%)	46 kPa	50	11	3	36
Di Marco et al[27] (abstract)	Palermo, Italy	Cross-sectional	NR	TE	69	NR[g]	41 (59.4%)	46.5 kPa	26	2	15	26
Hirooka et al[6] (pilot)	Ehime, Japan	Cross-sectional	2009–2010	RTE	60	0[h]	Any EV: 26 (43.3%)	8.24[g]	25	5	1	29
							Significant EV: 6[i]	9.67	6	14	0	40
Hirooka et al[6] (validation)	Ehime, Japan	Cross-sectional	2009–2010	RTE	190[j]	0[h]	47 (24.7%)	8.24[k]	46	9	1	134
Stefanescu et al[25]	Cluj-Napoca, Romania	Cross-sectional	NR	TE	137	NR	Any EV: 116 (84.7%)	46.4 kPa	97	6	19	15
							Significant EV: 9/80[i,l]	75 kPa	9	22	0	49
Vermehren et al[26]	Frankfurt, Germany	Cross-sectional	2009–2010	ARFI	166	NR	Any EV: NR	NR	NR	NR	NR	NR
							Significant EV: 60[d]	4.13 m/s	21	18	39	88
Takuma et al[7]	Okayama, Japan	Cross-sectional	2010–2011	ARFI	340	NR	Any EV: 132 (38.8%)	3.18 m/s	130	83	2	125
							Significant EV: 87[b]	3.30 m/s	86	17	1	28
Tanaka et al[30] (abstract)	Nishinomiya, Japan	Case-control	2011–2012	VTTQ	138	0	Any EV: 63 (45.6%)	2.73 m/s	55	13	8	62
							Significant EV: 19[d]	3.15 m/s	16	17	3	27
Ye et al[8]	Chongqing, China	Case-control	2011	ARFI	73[m]	NR	Any EV: 48 (65.7%)	3.16 m/s	40	5	8	20
							Significant EV:21[i]	3.39 m/s	17	11	4	41

FN, false negative; FP, false positive; NR, not reported; TN, true negative; TP, true positive.
[a]Originally 53 patients underwent SSM (including 3 who had unreliable findings), but EGD was available for only 44 patients (of whom 1 patient had an unreliable SSM).
[b]Significant EV defined as grade I EV with high-risk stigmata for bleeding and any grade II and III EV.
[c]There were 145 patients in the pilot study (published) and 24 patients in the validation cohort (obtained from investigators).
[d]Significant EV defined as any grade II and III EV.
[e]There were 104 patients, and the SSM measurement was unsuccessful in 8 patients (only 96 patients were included for estimating the diagnostic characteristics of spleen SSM).
[f]There were 100 patients included for estimating the diagnostic characteristics of spleen SSM.
[g]Overall, 176 patients underwent SSM (82 with F1/F2 fibrosis, 53 with F3/F4 fibrosis, 41 with clinical evidence of cirrhosis), of whom 25% had an unreliable TE.
[h]Excluded patients with a BMI greater than 25 (n = 6).
[i]Significant EV defined as any grade III EV.
[j]There were 210 patients with measurement of SSM, of whom 190 underwent EGD.
[k]Elastic ratio (proportion of small veins to that of splenic parenchyma).
[l]Separate cohort was presented at the European Association for Study of the Liver Annual Meeting 2011.
[m]There were 264 total patients who underwent SSM (including 60 controls), of whom 73 cirrhotic patients underwent EGD.

Table 2. Baseline Characteristics of Patients Included in the Systematic Review and Meta-analysis

Study	Mean age, *y* (SD)	Sex (% male)	Mean BMI, kg/m^2 (SD)	Cirrhosis (% total)	Child–Pugh score, A/B/C (%)	Etiology of CLD (% viral)
Al-Dahshan[23]	52.6 (8.2)	78.2	NR	100	NR	100
Borghi et al[28] (abstract)	62	74	26	100	A, 100%	47.5[a]
Bota et al[24]	59.1 (10.3)	60	NR	100	A/B/C, 45/43/12	50.3
Calvaruso et al[29] (abstract)	63.4 (9.0)	64.3	NR	100	A, 100%	100
Colecchia et al[5]	54 (40-84)[b]	71	25 (17.5-37.3)[b]	100	A, 100%	100
Di Marco et al[27] (abstract)	51.1 (13.8)	57	NR	100	NR	100
Hirooka et al[6] (pilot)	68 (8.9)	65	<25	80	A/B/C, 71/17/12	90
Hirooka et al[6] (validation)	62.1 (12.7)	53.8	<25	NR	B/C, 13/10	78.6
Stefanescu et al[25]	56 (31-76)[b]	56.2	26 (17.2-36.3)[b]	100	A/B/C, 65/28/7	NR[c]
Vermehren et al[26]	54 (11)	65.7	26 (5)	100	A/B+C, 54/46	48
Takuma et al[7]	67.8 (9.9)	52	23.5 (3.8)	100	A/B/C, 67/27/6	73.8
Tanaka et al[30]	59.2	50	23.0 (3.6)	59	NR	80
Ye et al[8]	39.3 (13.7)	59.8	21.9 (2.9)	100	NR	100

CLD, chronic liver disease; NR, not reported; SD, standard deviation.
[a]Percentage with hepatitis C virus.
[b]Median (range).
[c]Hepatitis C virus or alcoholic.

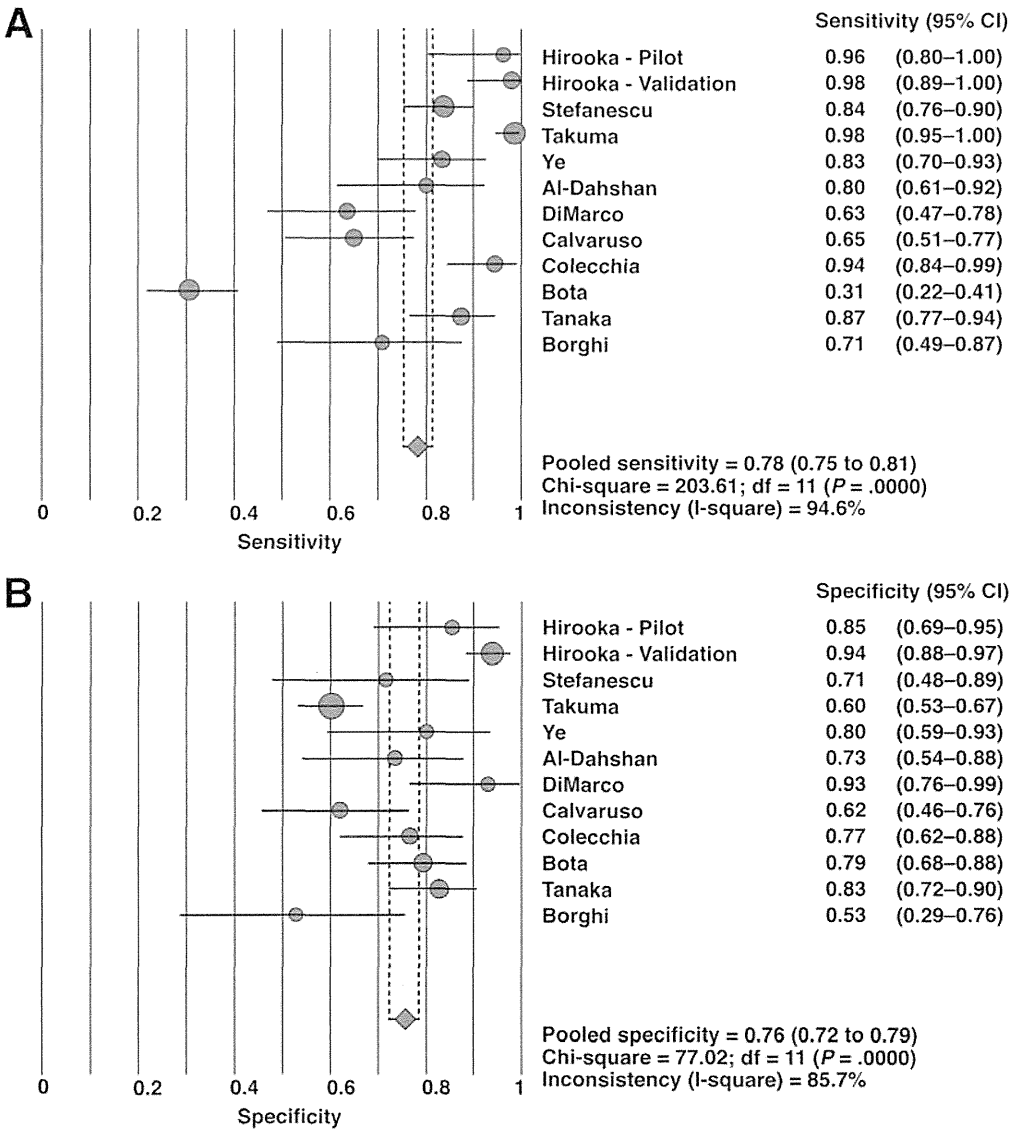

Figure 2. (*A*) Forest plots and meta-analyses of studies evaluating the sensitivity of SSM compared with EGD for the detection of any EVs in patients with chronic liver disease. (*B*) Forest plots and meta-analyses of studies evaluating the specificity of SSM compared with EGD for the detection of any EVs in patients with chronic liver disease.

There was evidence of considerable heterogeneity between studies, both qualitatively and quantitatively (I^2 for pooled sensitivity and specificity, 95% and 86%, respectively). On subgroup analysis, the heterogeneity could be explained on the location of study and technique of SSM (Table 3). Studies conducted in Asian populations showed a significantly better diagnostic performance of SSM, as compared with Western populations (diagnostic OR (95% CI): Asian vs Western, 51.4 (17.9–147.6) vs 7.1 (2.5–20.4), $P_{interaction} = .009$). RTE appeared to be significantly superior to TE and ARFI for SSM, although both studies that used RTE were performed in the same center (diagnostic OR (95% CI): TE vs RTE, 12.7 (4.6–35.5) vs 329.0 (71.9–1505.3), $P_{interaction} < .005$; ARFI vs RTE, 9.1 (1.3–62.3) vs 329.0 (71.9–1505.3), $P_{interaction} < .005$). There was no significant difference in the diagnostic accuracy of SSM based on the etiology of chronic liver disease.

Sensitivity analysis. On using the fitted bivariate regression model, the estimates of pooled sensitivity (OR, 85% [95% CI, 72%–93%]), specificity (OR, 78% [95% CI, 70%–85%]), positive LR (OR, 3.9 [95% CI, 2.7–5.7]), negative LR (OR, 0.2 [95% CI, 0.1–0.4]), diagnostic OR (21 [95% CI, 8–55]), and the hierarchical summary ROC (OR, 0.87 [95% CI, 0.84–0.89]), were not significantly different from the random-effects model.[19] On restricting analysis to 9 studies performed in patients with cirrhosis (in whom SSM presumably would be most applicable),[5,7,8,23–25,27–29] the pooled sensitivity and specificity was 75% (95% CI, 72%–78%) and 68% (95% CI, 64%–72%), with a diagnostic OR of 11.1 (95% CI, 4.3–28.7) (Table 3). On further analysis, restricting only to studies performed in patients with Child A compensated cirrhosis, the pooled sensitivity and specificity were 78% and 67%, respectively. Sensitivity analysis of only high-quality studies or studies published as full texts did not significantly improve the diagnostic performance of SSM. Because it was unclear whether there was overlap in the patient population in 2 studies,[27,29] we repeated analysis after excluding each of these studies sequentially, which did not significantly alter the results (data not shown).

Publication bias. On performing the Deeks' funnel plot asymmetry test, there was no evidence of significant publication bias ($P = .30$) (figure not shown).[22]

Table 3. Subgroup and Sensitivity Analysis Reporting the Diagnostic Test Performance Characteristics of SSM for the Detection of Esophageal Varices in Patients With Chronic Liver Disease

Variable	Subgroups	N	Sensitivity	I^2	Specificity	I^2	Positive LR	Negative LR	Diagnostic OR
Subgroup analysis									
Technique	TE	5	0.79 (0.74–0.83)	82	0.74 (0.67–0.81)	59	3.0 (1.9–4.8)	0.3 (0.2–0.5)	12.7 (4.6–35.5)
	ARFI	4	0.72 (0.66–0.77)	98	0.65 (0.60–0.70)	78	2.1 (1.4–3.1)	0.2 (0.04–1.6)	9.1 (1.3–63.0)
	RTE	2	0.97 (0.91–0.99)	0	0.92 (0.87–0.96)	57	10.5 (4.5–24.4)	0.03 (0.01–0.1)	329.0 (71.9–1505.3)
	VTTQ	1	0.88	NA	0.83	NA	5.2	0.1	37
Location	Asian	6	0.92 (0.89–0.95)	80	0.76 (0.72–0.80)	92	4.9 (2.6–9.2)	0.1 (0.04–0.2)	51.4 (17.9–147.6)
	European	6	0.66 (0.61–0.71)	95	0.74 (0.68–0.80)	66	2.4 (1.5–3.7)	0.4 (0.2–0.7)	7.1 (2.5–20.4)
Etiology of CLD	Viral	5	0.77 (0.71–0.83)	81	0.76 (0.68–0.82)	60	3.3 (2.0–5.4)	0.3 (0.2–0.5)	14.0 (4.7–41.9)
	Mixed	7	0.79 (0.75–0.82)	97	0.75 (0.72–0.79)	91	3.5 (2.1–6.1)	0.1 (0.03–0.6)	23.4 (5.5–117.9)
Sensitivity analysis									
Only cirrhosis		9	0.75 (0.72–0.78)	95	0.68 (0.64–0.72)	70	2.5 (1.9–3.2)	0.3 (0.1–0.5)	11.1 (4.3–28.7)
Only compensated/ Child A cirrhosis		3	0.78 (0.70–0.85)	88	0.67 (0.57–0.75)	53	2.2 (1.2–3.9)	0.3 (0.1–1.0)	7.3 (1.2–42.9)
Publication type	Full text	8	0.80 (0.77–0.83)	96	0.75 (0.72–0.79)	88	3.8 (2.4–6.1)	0.1 (0.03–0.5)	30.9 (8.0–119.0)
	Abstract	4	0.73 (0.66–0.79)	73	0.76 (0.68–0.82)	82	2.9 (1.4–6.2)	0.4 (0.2–0.7)	8.6 (2.2–33.6)
Study quality	High	6	0.80 (0.76–0.83)	97	0.75 (0.71–0.79)	90	3.9 (2.1–7.1)	0.1 (0.01–0.7)	42.1 (6.4–277.6)
	Low	6	0.76 (0.70–0.81)	70	0.76 (0.70–0.81)	76	3.0 (1.8–5.1)	0.3 (0.2–0.5)	10.1 (4.0–25.9)

CLD, chronic liver disease.

Spleen Stiffness for Detection of Clinically Significant Esophageal Varices

Nine studies provided relevant data on the diagnostic accuracy for identifying patients with clinically significant EV.[6–8,24–26,28–30] Clinically significant varices were variably defined in the included studies as 1 of 3: grade I EV with high-risk stigmata for bleeding and any grades II and III EV (2 studies),[7,28] any grades II or III EV (4 studies),[24,26,29,30] or any grade III EV (3 studies).[6,8,25]

On meta-analysis of these studies, the sensitivity and specificity of SSM for detecting clinically significant

varices in patients with chronic liver disease was 81% (95% CI, 76%–86%) and 66% (95% CI, 61%–69%), respectively (Figure 3*A* and *B*). The diagnostic OR was 12.6 (95% CI, 5.50–28.73), and the AUROC was 0.80 (95% CI, 0.75–0.85) (Supplementary Figure 3). Significant heterogeneity was observed in the analysis, which also could be explained based on location of study and technique of SSM (Table 4).

Discussion

In this systematic review and meta-analysis of 12 studies on the diagnostic performance of current techniques of SSM for the detection of EV in patients with chronic liver disease, we observed that the summary estimates for sensitivity (78%) and specificity (76%) were good, and the LRs for the presence or absence of EV based on SSM were modest. Likewise, the diagnostic performance of SSM for detecting the presence of clinically significant EV also was good, but not at levels that would suggest low false-positive and false-negative diagnostic rates were these techniques used in clinical practice. The performance was similar on using the fitted bivariate regression model[18] as well as on limiting analysis to patients with cirrhosis, including compensated cirrhosis, in which there is the greatest need for an easily applicable noninvasive test given differences in the prognosis of patients with compensated cirrhosis, with and without varices.[33] For both analyses, we observed considerable heterogeneity, which could be explained based on the technique of SSM and the location where the study was performed.

Portal hypertension results in splenic congestion, which increases spleen stiffness. In addition, portal hypertension also induces architectural changes in the splenic arteries and veins and induces splenic fibrosis.[34,35] Studies have shown excellent correlation between SSM and portal hypertension as measured by hepatic venous pressure gradient,[5,6] lending support to the biologic plausibility of measuring spleen stiffness for detecting the presence and size of EV. On the other hand, liver elastography measures hepatic fibrosis, which only correlates with the fixed component of portal hypertension related to intrahepatic resistance, but is unable to account for the dynamic component related to hyperdynamic splanchnic circulation and portal venous blood flow.[9] As compared with liver stiffness measurement, the diagnostic performance of SSM was significantly better. In a systematic review of

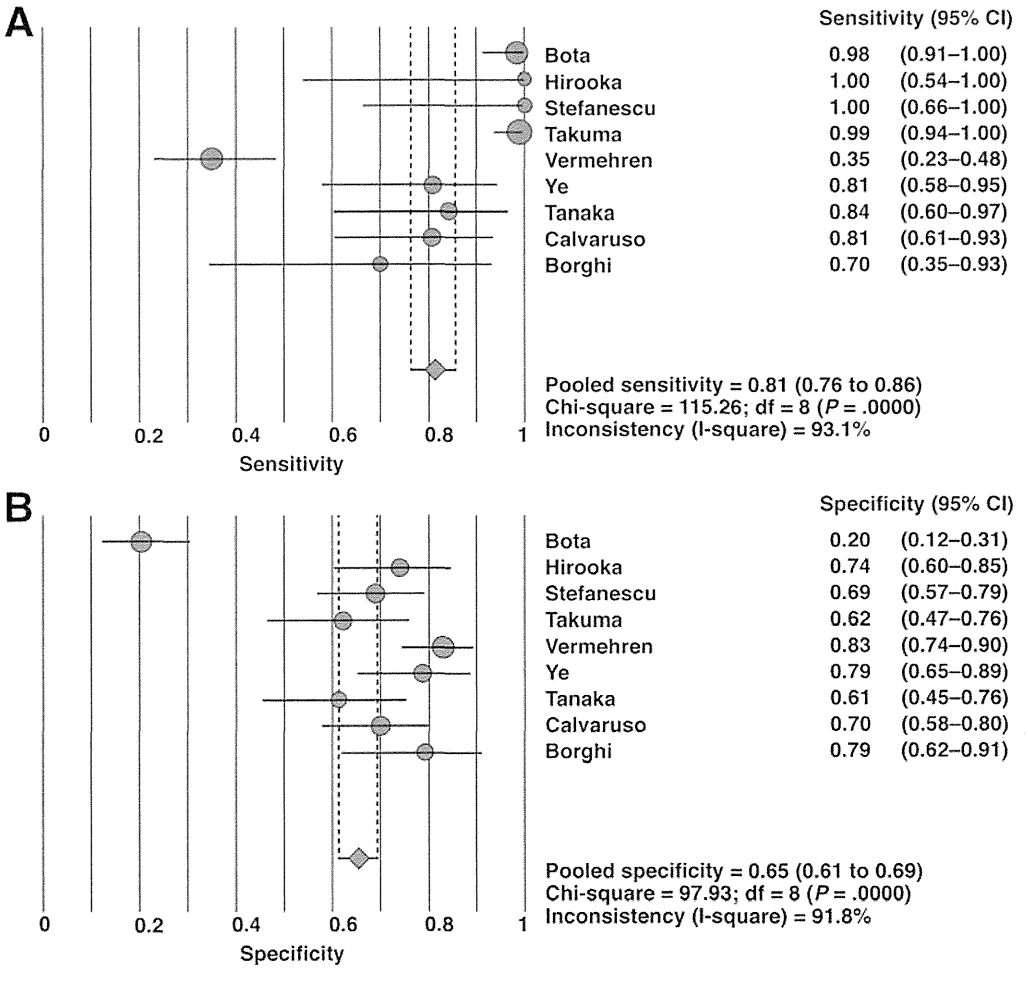

Figure 3. (*A*) Forest plots and meta-analyses of studies evaluating the sensitivity of SSM compared with EGD for the detection of clinically significant EVs in patients with chronic liver disease. (*B*) Forest plots and meta-analyses of studies evaluating the specificity of SSM compared with EGD for the detection of clinically significant EVs in patients with chronic liver disease.

Table 4. Subgroup Analysis Reporting the Diagnostic Test Performance Characteristics of SSM for the Prediction of Clinically Significant EVs in Patients With Chronic Liver Disease

	N	Sensitivity	I^2	Specificity	I^2	Positive LR	Negative LR	Diagnostic OR
Technique								
TE	2	0.86 (0.70–0.95)	69	0.69 (0.61–0.77)	0	2.9 (2.2–3.8)	0.2 (0.1–0.5)	11.8 (4.2–33.0)
ARFI	5	0.80 (0.74–0.85)	96	0.63 (0.57–0.68)	96	2.4 (1.2–4.8)	0.2 (0.04–0.8)	13.0 (3.4–50.1)
RTE	1	1.00	NA	0.74	NA	3.9	0	NA
VTTQ	1	0.84	NA	0.61	NA	2.1	0.3	8.3
Location								
Asian	4	0.94 (0.88–0.97)	76	0.70 (0.63–0.76)	43	2.8 (2.2–3.6)	0.1 (0.04–0.4)	22.7 (6.9–74.2)
European	5	0.71 (0.64–0.78)	95	0.63 (0.58–0.68)	96	2.3 (1.3–4.1)	0.3 (0.1–0.8)	7.5 (3.0–19.1)
CLD etiology								
Viral	3	0.83 (0.70–0.92)	16	0.74 (0.67–0.80)	0	3.2 (2.4–4.2)	0.2 (0.1–0.4)	13.1 (5.9–29.1)
Mixed	6	0.81 (0.75–0.86)	96	0.62 (0.56–0.66)	94	2.2 (1.4–3.7)	0.2 (0.04–0.7)	12.9 (3.7–44.6)

CLD, chronic liver disease.

12 studies on the diagnostic accuracy of TE-based liver stiffness measurement, the diagnostic OR for detecting the presence of any and large EV was 7.5 (95% CI, 4.5–12.7) and 8.8 (95% CI, 5.9–13.2), respectively.[36] The comparable values of diagnostic ORs for SSM were 19.3 and 12.6, respectively.

There are several techniques for the measurement of spleen stiffness. The 2 most commonly studied are TE and ARFI. Although both measure spleen elasticity, there are minor differences in the method of measurement, which result in different units in which spleen stiffness is reported; the former reports stiffness in kilopascals, while the latter, in which shear wave velocity is evaluated to assess the elastic properties of target tissues, reports stiffness in meters per second.[37] We observed that the diagnostic performance of both these techniques is comparable. Although TE requires a dedicated device and a mandatory ultrasound examination of the spleen before SSM, ARFI can be performed using standard ultrasound equipment; however, there is limited validation of ARFI and measures of quality are not well defined.[9] On the other hand, RTE, a qualitative, ultrasound-based technique that measures the relative elasticity of splenic parenchyma in relation to small splenic veins, appeared to perform better than the other techniques.[6] Of note, both the studies that reported on the performance of RTE were performed in the same center, with different patients. Magnetic resonance elastography of the spleen is also feasible, and may be useful for detecting the presence of EV in patients with advanced hepatic fibrosis. In a pilot study in our center, magnetic resonance elastography of the spleen was technically successful in healthy volunteers and patients with chronic liver disease, correlated well with liver stiffness, and at a cut-off value of 10.5 kPa or greater was able to identify all patients with EV.[38]

We also observed that the diagnostic performance of SSM was better across all Asian studies as compared with studies performed in Western centers. Although the diagnostic OR for detecting EV was 51 in Asian studies, it was 7 in Western studies. This observed difference is related potentially to differences in body size and body habitus across these populations. The success of all ultrasound-based techniques for measuring SSM is dependent on how well the waves travel through tissue; the presence of abdominal fat is a major limitation in the performance of these tests. Although Hirooka et al[6] excluded patients with a BMI greater than 25 kg/m^2 from this test, other Asian subjects tended to have a smaller mean BMI (range of mean BMI, 21.9–23.5 kg/m^2), whereas in Western studies, the mean BMI of the studied population was higher (range of mean BMI, 25.0–26.0 kg/m^2). It is unknown whether there are inherent differences in the spleen elasticity across Asian and European subjects.

The strengths of our meta-analysis were the comprehensive assessment of the diagnostic accuracy of SSM, measured using different techniques, across different patient and disease characteristics, to provide a more real-world estimate of the test performance. In addition, through subgroup analysis, we were able to identify systematic differences in the performance characteristics of the test across Asian and Western population. We also sought missing data from individual investigators, and, hence, were able to decrease the risk of reporting bias, which is a major limitation of studies on diagnostic test accuracy.

There were several limitations that need to be considered while interpreting the results of our analysis. First, because of differences in techniques of assessing SSM, we were not able to define a diagnostic threshold, which may be used to provide the greatest accuracy in predicting the presence or size of EV. Even within a specific technique, differences in diagnostic threshold values may account for the heterogeneity observed with the results. The choice of diagnostic threshold may be explicit, identified through natural observation, or derived on the basis of disease prevalence. Hence, even for a specific technique, it is difficult to estimate a diagnostic threshold of SSM based on the limited number of studies. Second, although the number of published studies examining SSM was small given the

recent emergence of this technology, it remains possible that investigations showing poor reproducibility or accuracy have not been published because of negative results. We tried to minimize the effect of publication bias by including reports from conference proceedings, including non-English language literature in our search and contacting individual investigators. Third, although EGD is regarded as the standard for assessing EV, there is significant interobserver variability, which limits the validity of gold standard against which SSM was compared.[39] Fourth, through a validated assessment of methodologic quality of the individual studies, we identified that most of the reported studies provided insufficient information on whether the results of the SSM were interpreted while blinded to EGD results, or vice versa, putting them at risk for review bias. Similarly, the time period between performance of EGD and SSM was not clear in 6 studies, putting them at risk for disease progression bias. In addition, the studies did not adequately study the spectrum of patients who were most likely to receive this test (ie, patients with compensated or decompensated cirrhosis), putting them at risk for spectrum bias. In particular, the study by Bota et al[24] included a high proportion of patients with Child B and C cirrhosis, and hence may have resulted in a low sensitivity.

In conclusion, based on the systematic review and meta-analysis across different centers, incorporating different stages and etiologies of chronic liver disease, we observed that the current techniques of SSM, although promising, are suboptimal at this time to replace EGD as the screening modality of choice for detecting the presence and size of EV. Regardless, the limited utility of these techniques in obese patients remains a cause for concern for their widespread applicability, especially in light of the increasing incidence of nonalcoholic steatohepatitis as a cause of cirrhosis. Future, well-designed prospective studies, in diverse settings in patients with compensated or decompensated cirrhosis, evaluating the diagnostic accuracy of SSM in detecting the presence of clinically significant varices, are required.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2013.09.013.

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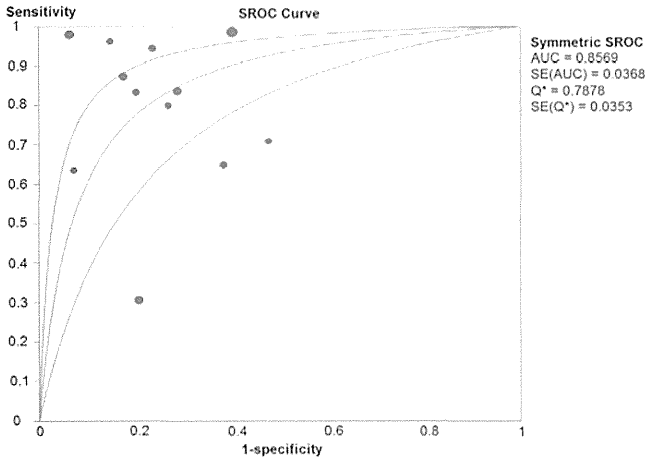
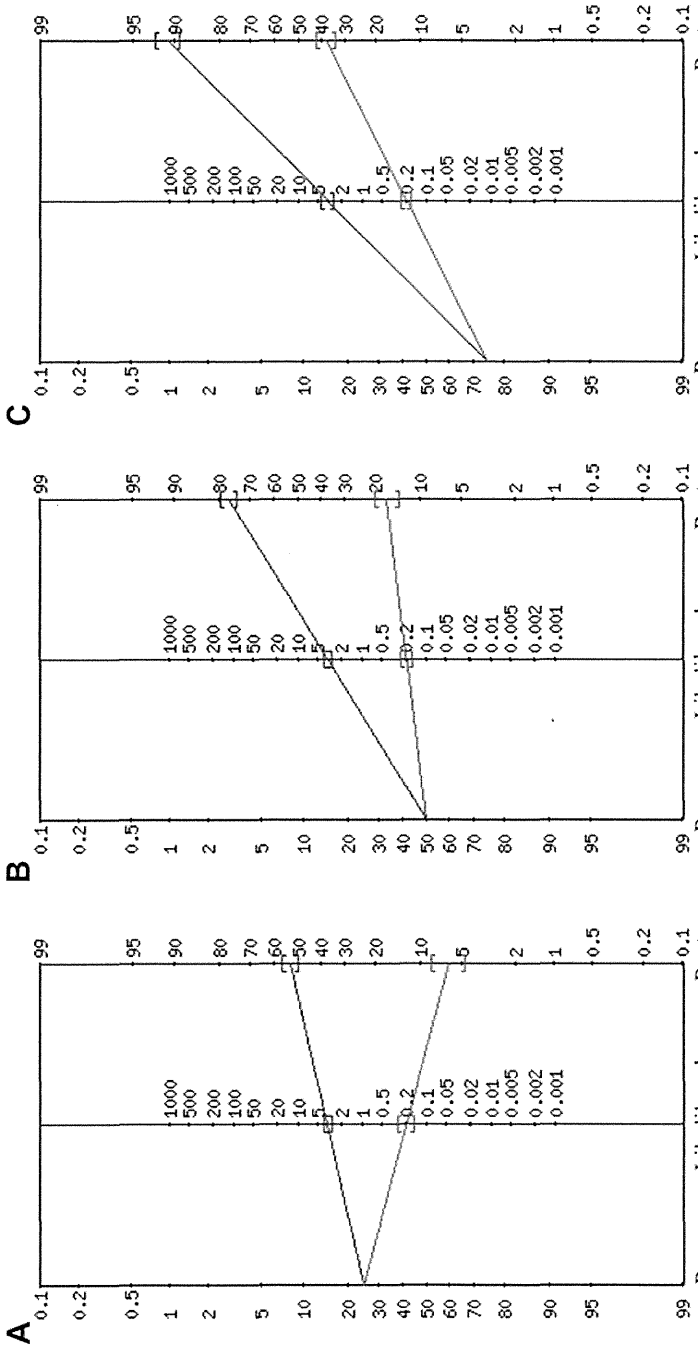
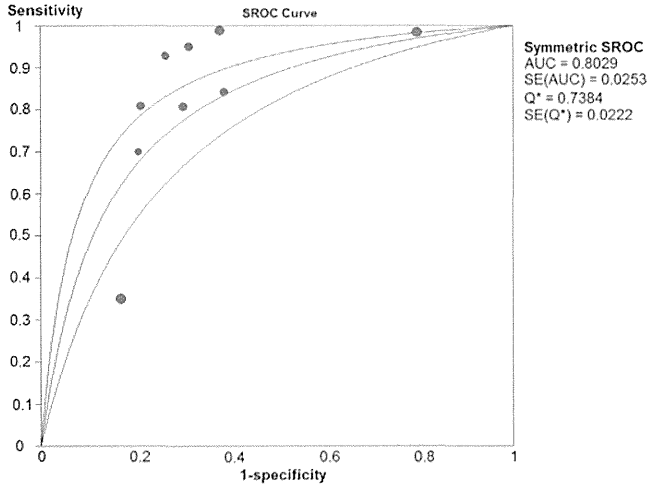
Conflicts of interest
The authors disclose no conflicts.



Supplementary Figure 1. Summary ROC curve for all 12 studies examining SSM compared with EGD for the detection of any EVs. SE, standard error.



Supplementary Figure 2. Fagan nomogram estimating the post-test probability of EV, depending on the pretest clinical suspicion and results of spleen elastography. (*A*) With a pretest probability of EV of 25% (low clinical suspicion, as observed in patients with compensated cirrhosis), the post-test probability of EV, given a negative SSM (*red*), is 6%, and given a positive SSM (*blue*), is 53%. (*B*) With a pretest probability of EV of 50% (as observed in patients with decompensated cirrhosis), the post-test probability of EV, given a negative SSM (*red*), is 16%, and given a positive SSM (*blue*), is 78%. (*C*) With a hypothetical pretest probability of EV of 75%, the posttest probability of EV, given a negative SSM (*red*), is 36% and given a positive SSM (*blue*), is 91%.



Supplementary Figure 3. Summary ROC curve for 9 studies examining SSM compared with EGD for the detection of clinically significant EVs. SE, standard error.

Supplementary Table 1. Quality Assessment of the Included Studies Using the QUADAS

QUADAS assessment items	Al-Dahshan[23]	Bota et al[24]	Borghi et al[28]	Calvaruso et al[29]	Colecchia et al[5]	DiMarco et al[27]	Hirooka et al[6]	Stefanescu et al[25]	Vermehren et al[26]	Takuma et al[7]	Tanaka et al[30]	Ye et al[8]
Was the spectrum of patients representative of the patients who will receive the test in practice? (spectrum bias)	N	N	Y	Y	Y	U	N	Y	Y	Y	U	N
Were selection criteria clearly described?	Y	Y	N	N	Y	N	Y	N	Y	Y	N	Y
Is the reference standard likely to correctly classify the target condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the 2 tests? (disease progression bias)	U	Y	U	Y	Y	U	Y	U	N	Y	U	U
Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis? (partial verification bias)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N
Did patients receive the same reference standard regardless of the index test result? (differential verification bias)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the reference standard independent of the index test (ie, the index test did not form part of the reference standard)? (incorporation bias)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the execution of the index test described in sufficient detail to permit replication of the test?	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y
Was the execution of the reference standard described in sufficient detail to permit its replication?	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y
Were the index test results interpreted without knowledge of the results of the reference standard? (review bias)	U	Y	Y	U	Y	U	U	U	U	Y	U	Y
Were the reference standard results interpreted without knowledge of the results of the index test? (review bias)	Y	Y	Y	U	Y	U	U	U	U	U	U	U
Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y
Were uninterpretable/intermediate test results reported?	N	Y	N	Y	Y	U	Y	Y	Y	N	N	N
Were withdrawals from the study explained?	U	U	U	U	Y	U	Y	Y	Y	U	N	U
Total score (maximum, 14)	9	12	7	8	14	4	11	10	11	11	6	8

NOTE. Results of the QUADAS assessment items are interpreted as follows: Y, yes; N, no; U, unclear. One point is awarded for each yes response.
QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

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Original Article

Prospective comparison of real-time tissue elastography and serum fibrosis markers for the estimation of liver fibrosis in chronic hepatitis C patients

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Aim: Real-time tissue elastography (RTE) is a non-invasive method for the measurement of tissue elasticity using ultrasonography. Liver fibrosis (LF) index is a quantitative method for evaluation of liver fibrosis calculated by RTE image features. This study aimed to investigate the significance of LF index for predicting liver fibrosis in chronic hepatitis C patients.

Methods: In this prospective study, 115 patients with chronic hepatitis C who underwent liver biopsy were included, and the diagnostic accuracy of LF index and serum fibrosis markers was evaluated.

Results: RTE imaging was successfully performed on all patients. Median LF index in patients with F0–1, F2, F3 and F4 were 2.61, 3.07, 3.54 and 4.25, respectively, demonstrating a stepwise increase with liver fibrosis progression ($P < 0.001$). LF index (odds ratio [OR] = 5.3, 95% confidence interval [CI] = 2.2–13.0) and platelet count (OR = 0.78, 95% CI = 0.68–0.89) were independently associated with the presence of advanced fibrosis (F3–4). Further, LF index was independently associated with the presence of minimal fibrosis (F0–1) (OR = 0.25, 95% CI = 0.11–0.55). The area under the receiver–operator curve (AUROC) of LF index for predicting advanced fibrosis (0.84) was superior to platelets (0.82), FIB-4 index (0.80) and aspartate aminotransferase/platelet ratio index (APRI) (0.76). AUROC of LF index (0.81) was superior to platelets (0.73), FIB-4 index (0.79) and APRI (0.78) in predicting minimal fibrosis.

Conclusion: LF index calculated by RTE is useful for predicting liver fibrosis, and diagnostic accuracy of LF index is superior to serum fibrosis markers.

Key words: chronic hepatitis C, fibrosis, liver fibrosis index, real-time tissue elastography

INTRODUCTION

AN ADVANCED STAGE of liver fibrosis in chronic hepatitis C (CHC) is associated with hepatocellular carcinoma development and complications such as esophageal variceal bleeding and liver failure.[1,2] Therefore, accurate evaluation of the stage of liver fibrosis is most important in clinical practice. Liver biopsy is considered to be the golden standard for diagnosis of liver fibrosis.[3–5] However, this method may be inaccurate because of sampling errors and interobserver variations.[6,7]

Improvements in a variety of non-invasive methods for evaluating liver fibrosis have recently emerged as alternatives to liver biopsy. Liver fibrosis was reportedly predicted by measurement of liver stiffness using transient elastography[8,9] and acoustic radiation force impulse (ARFI).[10,11] As assessed by blood laboratory tests, the aspartate aminotransferase (AST)/alanine

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aminotransferase (ALT) ratio,[12] AST/platelet ratio index (APRI),[13,14] and FIB-4 index[15,16] have been reported to be useful for the prediction of liver fibrosis. We previously reported that the FIB-4 index is useful for the prediction of liver fibrosis progression.[17]

Real-time tissue elastography (RTE) is a non-invasive method for the measurement of tissue elasticity using ultrasonography.[18] RTE calculates the relative hardness of tissue from the degree of tissue distortion and displays this information as a color image. RTE was recently reported to be useful for predicting liver fibrosis.[19,20] To increase the objectivity of the evaluation, an image analysis method to evaluate the strain image features and a new algorithm to deliver an index were proposed. Liver fibrosis (LF) index is a quantitative method for evaluation of liver fibrosis that is calculated by nine RTE image features, and the significance of LF index for predicting liver fibrosis has been reported.[21,22]

In the present study, we prospectively investigated the significance of LF index calculated by RTE for the prediction of liver fibrosis in CHC patients. Further, diagnostic accuracy for liver fibrosis was compared between LF index and serum fibrosis markers.

METHODS

Patients

A TOTAL OF 127 consecutive patients with CHC were prospectively investigated. All patients underwent liver biopsy at Musashino Red Cross Hospital between February 2011 and November 2012. Exclusion criteria comprised the following: (i) co-infection with hepatitis B virus ($n = 1$); (ii) co-infection with HIV ($n = 1$); (iii) history of autoimmune hepatitis or primary biliary cirrhosis ($n = 3$); (iv) alcohol abuse (intake of alcohol equivalent to pure alcohol ≥40 g/day) ($n = 0$); (v) portal tracts of biopsy sample of less than five ($n = 7$); and (vi) presence of serious heart disease ($n = 0$). After exclusion, 115 patients were enrolled in this study. Written informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the institutional ethics review committees (application no. 24007).

Histological evaluation

Liver biopsy specimens were laparoscopically obtained using 13-G needles ($n = 93$). When laparoscopy was not conducted due to a history of upper abdominal surgery, percutaneous ultrasound-guided liver biopsy was performed using 15-G needles ($n = 22$). Specimens were fixed, paraffin-embedded, and stained with hematoxylin–eosin and Masson-trichrome. A biopsy sample with minimum portal tracts of five was required for diagnosis. All liver biopsy samples were independently evaluated by two senior pathologists who were blinded to the clinical data. Fibrosis staging was categorized according to the METAVIR score:[23] F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Activity of necroinflammation was graded on a scale of 0–3: A0, no activity; A1, mild activity; A2, moderate activity; and A3, severe activity. Percentage of steatosis was quantified by determining the average proportion of hepatocytes affected by steatosis and graded on a scale of 0–3: grade 0, no steatosis; grade 1, 1–33%; grade 2, 34–66%; and grade 3, 67% and over.

Clinical and biological data

The age and sex of the patients were recorded. Serum samples were collected within 1 day prior to liver biopsy and the following variables were obtained through serum sample analysis: AST, ALT and platelet count. FIB-4 index and APRI were calculated according to the published formula appropriate to each measure.[13,15]

RTE and LF index

Real-time tissue elastography was performed using HI VISION Preirus (Hitachi Aloka Medical, Tokyo, Japan) and the EUP-L52 linear probe (3–7 MHz; Hitachi Aloka Medical) within 3 days of liver biopsy. RTE was performed on the right lobe of the liver through the intercostal space. An RTE image was induced by heartbeats. Five RTE images were collected for each patient and analyzed to calculate nine image features. RTE method and the equation that calculates LF index using nine image features has been previously detailed.[22] Results are expressed as mean LF index of all measurements. Two hepatologists (N. T. and K. Tsuchiya, with 8 and 16 years of experience, respectively) performed RTE. In 32 patients with CHC, LF index was measured independently by two examiners. The correlation coefficient of LF index between two examiners was 0.85 ($P \leq 0.001$).

Statistical analysis

Correlations between LF index and histological fibrosis stage were analyzed using Spearman's rank correlation coefficients. Categorical variables were compared using Fisher's exact test, and continuous variables were compared using Mann–Whitney *U*-test. $P < 0.05$ was considered statistically significant. Logistic regression was

used for multivariate analysis. Receiver-operator curves (ROC) were constructed, and the area under the ROC (AUROC) was calculated. Optimal cut-off values were selected, to maximize sensitivity, specificity and diagnostic accuracy. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated by using cut-offs obtained by ROC. SPSS software ver. 15.0 (SPSS, Chicago, IL, USA) was used for analyses.

RESULTS

Patient characteristics

THE CHARACTERISTICS OF all 115 patients are listed in Table 1. F0–1 was diagnosed in 52 cases (45%), F2 in 31 (27%), F3 in 20 (17%) and F4 in 12 (11%). Mean values of LF index of F0 (2.62) and F1 (2.60) were not significantly different ($P = 0.9$), and only six patients with F0 were included in this study. Therefore, patients with F0 and F1 were integrated for the analysis. RTE imaging was successfully performed in all patients, and LF index was calculated.

Relationship between histological findings and LF index by RTE

The median value of LF index compared with the METAVIR fibrosis stage is shown in Figure 1. Median LF index in patients with F0–1, F2, F3 and F4 were 2.61, 3.07, 3.54 and 4.25, respectively, demonstrating a stepwise increase with liver fibrosis progression ($P < 0.001$). LF index of each fibrosis stage significantly differed from each other (F0–1 vs F2, $P < 0.001$; F0–1 vs F3, $P < 0.001$; F0–1 vs F4, $P < 0.001$; F2 vs F3, $P = 0.009$; F2 vs F4, $P = 0.001$). On the other hand, mean values of LF index in patients with steatosis grade 0, 1 and 2 were 2.99, 3.29 and 2.60, respectively, demonstrating no significant correlation (Fig. 2a). LF index was compared with steatosis grade for each fibrosis stage. LF index was not significantly different between patients with steatosis and without steatosis (Fig. 2b).

Liver fibrosis index was compared with histological activity. A significant correlation existed between histological activity and fibrosis stage. Therefore, the relationship between LF index and histological activity was examined by each fibrosis stage. In patients with F0–1, the mean LF index of A1, A2 and A3 was 2.60, 2.58 and 2.40, respectively, demonstrating no significant correlation. Similarly, in patients with F2, F3 and F4, there was no significant correlation between LF index and histological activity (Fig. 3).

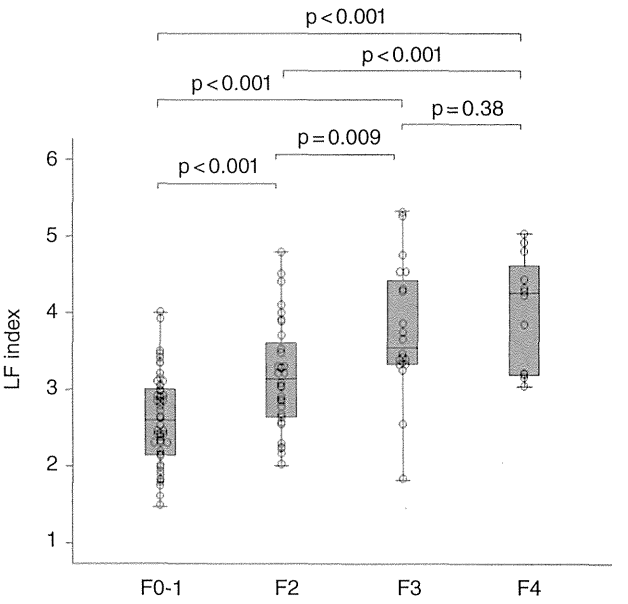

Figure 1 Correlation between liver fibrosis (LF) index calculated by real-time tissue elastography and fibrosis stage. Box plot of the LF index is shown according to each fibrosis stage. The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and error bar indicates minimum and maximum non-extreme values.

Table 1 Patient characteristics

Characteristics	Patients ($n = 115$)
Female/male	68/47
Age (years)	57.9 ± 10.9
AST (IU/L)	55.7 ± 44.9
ALT (IU/L)	63.2 ± 56.3
Platelet counts ($\times 10^9$/L)	162 ± 53
Portal tracts of biopsy samples	12.6 ± 5.0
Fibrosis stage	
F0–1 (%)	51 (44)
F2 (%)	32 (28)
F3 (%)	20 (17)
F4 (%)	12 (11)
Histological activity	
A0 (%)	0 (0)
A1 (%)	75 (65)
A2 (%)	34 (30)
A3 (%)	6 (5)
Steatosis grade	
Grade 0 (%)	65 (57)
Grade 1 (%)	47 (41)
Grade 2 (%)	3 (2)
Grade 3 (%)	0 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

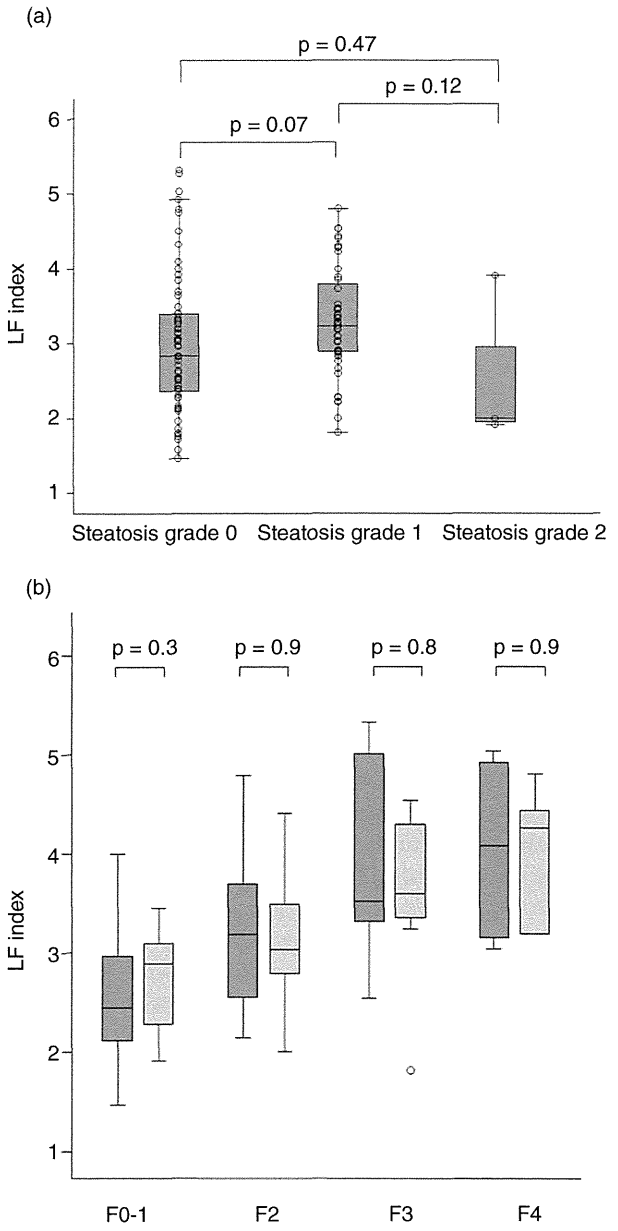

Figure 2 (a) Correlation between liver fibrosis (LF) index and steatosis grade. Box plot of the LF index is shown according to each steatosis grade. The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and error bar indicates minimum and maximum non-extreme values. (b) Box plot of LF index for each fibrosis stage in relation to degree of steatosis grade. The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and error bar indicates minimum and maximum non-extreme values. Dark grey bar chart indicates steatosis grade 0. Light grey bar chart indicates steatosis grade 1–2.

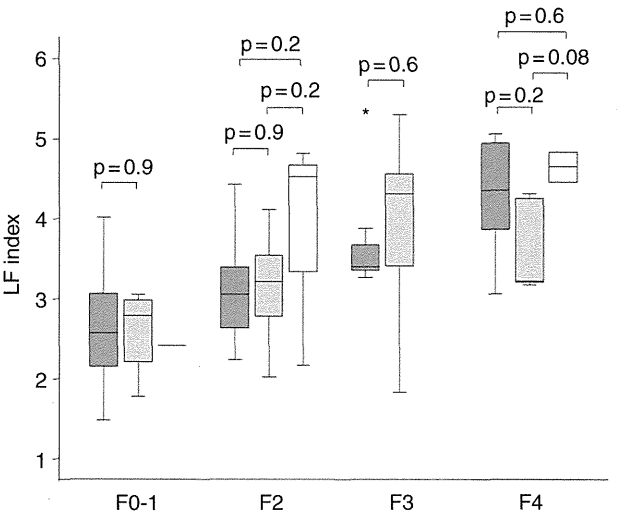

Figure 3 Box plot of liver fibrosis (LF) index for each fibrosis stage in relation to degree of necroinflammatory activity. The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The line through the box indicates the median value, and error bar indicates minimum and maximum non-extreme values. Dark grey bar chart indicates activity grade 1. Light grey bar chart indicates activity grade 2. White bar chart indicates activity grade 3.

Comparison of variables associated with the presence of advanced fibrosis (F3–4) by univariate and multivariate analysis

Variables associated with the presence of advanced fibrosis (F3–4) were assessed by univariate and multivariate analysis (Table 2). The variables of age ($P = 0.03$) and LF index ($P < 0.001$) were significantly higher, and the variable of platelets ($P < 0.001$) was significantly lower in patients with advanced fibrosis than in patients with F0–2. Multivariate analysis showed that LF index (odds ratio [OR] = 5.3, 95% confidence interval [CI] =2.2–13.0) and platelets (OR = 0.78, 95% CI = 0.68–0.89) were independently associated with the presence of advanced fibrosis.

Comparison of variables associated with the presence of minimal fibrosis (F0–1) by univariate and multivariate analysis

Variables associated with the presence of minimal fibrosis (F0–1) were assessed by univariate and multivariate analysis (Table 3). The variables of age ($P < 0.001$), AST ($P = 0.02$) and LF index ($P < 0.001$) were significantly lower, and the variable of platelets ($P < 0.001$) was significantly higher in F0–1 patients than F2–4 patients.

Table 2 Variables associated with the presence of advanced fibrosis (F3–4) by univariate and multivariate analysis

	F0–2 ($n = 83$)	F3–4 ($n = 32$)	*P*-value (Univariate)	Odds ratio (95% CI) (Multivariate)
Age (years)	56.6 ± 10.9	61.3 ± 10.4	0.03	
Sex (female/male)	51/32	17/15	0.41	
AST (IU/L)	52.3 ± 43.3	64.4 ± 48.3	0.19	
ALT (IU/L)	62.9 ± 60.6	63.9 ± 44.2	0.93	
Platelets ($\times 10^9$/L)	179 ± 47	117 ± 42	<0.001	0.78 (0.68–0.89)
LF index	2.81 ± 0.69	3.86 ± 0.81	<0.001	5.30 (2.16–13.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; LF, liver fibrosis.

Multivariate analysis showed that LF index was independently associated with the presence of minimal fibrosis (OR = 0.25, 95% CI = 0.11–0.55).

Diagnostic accuracy of RTE and serum fibrosis markers

Receiver–operator curves of LF index, platelets, FIB-4 index and APRI for predicting advanced fibrosis (F3–4), and minimal fibrosis (F0–1) were plotted, as shown in Figure 4. AUROC of LF index for predicting advanced fibrosis (0.84) was superior to platelets (0.82), FIB-4 index (0.80) and APRI (0.76). Similarly, for predicting minimal fibrosis, AUROC of LF index (0.81) was superior to platelets (0.73), FIB-4 index (0.79) and APRI (0.78). The corresponding sensitivities, specificities, PPV and NPV are detailed in Table 4.

DISCUSSION

IMPROVEMENTS IN VARIOUS methods for prediction of liver fibrosis have recently emerged as alternatives to liver biopsy. RTE is a non-invasive method for the measurement of tissue elasticity using ultrasonography. The utility of RTE for evaluating liver fibrosis is reported in a few studies.[18–22] However, for utilizing LF index, one of the equations used to calculate tissue elasticity by RTE is still unclear. The aim of this study was to investigate the significance of LF index for the prediction of liver fibrosis in CHC patients.

In this prospective study, we found that LF index is a useful predictive factor for diagnosis of the fibrosis stage in CHC patients. Increase in LF index significantly correlated with progression of the fibrosis stage and LF index was able to predict the presence of advanced fibrosis and minimal fibrosis. Previous studies reported the utility of LF index for prediction of the liver fibrosis stage.[21,22] In this study, LF index differed significantly between patients with F0–1 and F2; thus, LF index was especially useful for prediction of minimal fibrosis. This may be due to a sufficient number of patients with F0–1 and F2 included in the present study. This is an advantage of LF index because other quantitative methods by RTE could not discriminate patients with F0–1 and F2.[19,20] On the other hand, there is a possibility that a similar result may be obtained for differentiation of F3 and F4 if a large number of patients with advanced fibrosis was included.

Previous studies did not compare the diagnostic accuracy of LF index and serum fibrosis markers. We revealed that LF index performed better than serum fibrosis

Table 3 Variables associated with the presence of minimal fibrosis (F0–1) by univariate and multivariate analysis

	F0–1 ($n = 51$)	F2–4 ($n = 64$)	*P*-value (Univariate)	Odds ratio (95% CI) (Multivariate)
Age (years)	54.0 ± 11.9	61.0 ± 9.0	<0.001	
Sex (female/male)	31/20	37/27	0.74	
AST (IU/L)	44.5 ± 42.6	64.6 ± 44.9	0.02	
ALT (IU/L)	53.0 ± 56.3	71.3 ± 55.5	0.08	
Platelets ($\times 10^9$/L)	186 ± 47	142 ± 50	<0.001	
LF index	2.60 ± 0.59	3.51 ± 0.84	<0.001	0.25 (0.11–0.55)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; LF, liver fibrosis.

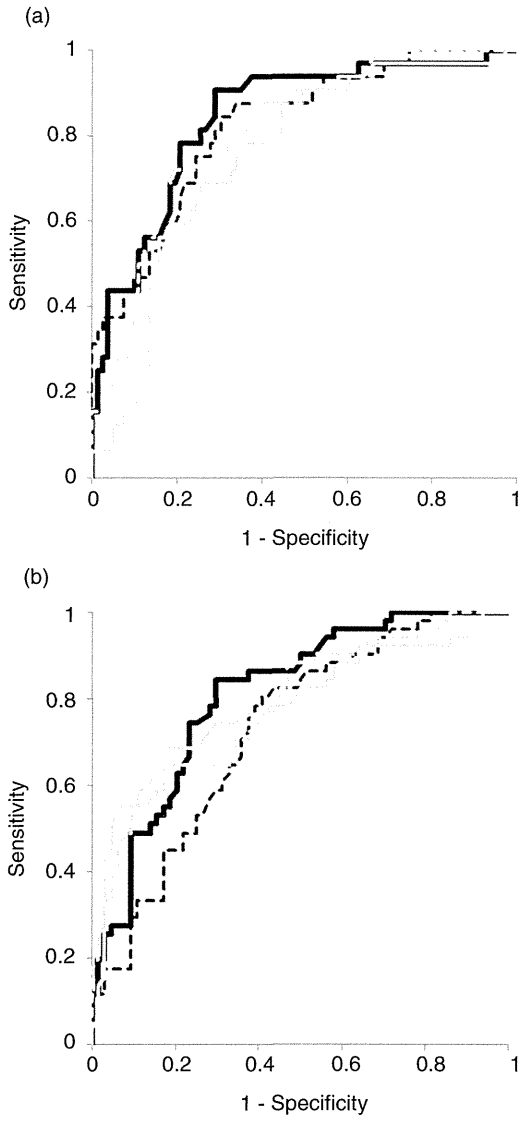

Figure 4 Receiver–operator curves (ROC) of liver fibrosis (LF) index and serum fibrosis markers. (a) ROC for diagnosis of significant fibrosis (F3–4). (b) ROC for diagnosis of minimal fibrosis (F0–1). —, LF index; ····, platelets; , aspartate aminotransferase-to-platelet ratio index; , FIB-4 index.

markers based on blood laboratory tests for predicting liver fibrosis.

Transient elastography has been most commonly used to measure liver stiffness and is established in clinical practice to evaluate liver fibrosis.[8,9] RTE exhibits some advantages compared with transient elastography. In this study, RTE imaging was successfully performed in all patients, and LF index was calculated. Although transient elastography has high diagnostic capabilities when it comes to liver fibrosis, measurements are sometimes impossible in patients with severe obesity and ascites.[24] Reproducibility of transient elastography was reportedly lower in patients with steatosis, inflammation, increased body mass index and lower degrees of liver fibrosis.[25–27] On the other hand, LF index is measured by ultrasound guidance that facilitates the identification of a suitable location for elastographic measurement, thereby resulting in a higher number of patients with valid results.

Unlike transient elastography, another advantage of LF index is that the results are not influenced by the presence of inflammation and steatosis. It was reported that LF index is not useful in patients with steatosis.[22] However, LF index was not significantly different between patients with and without steatosis in the present study even after stratification by fibrosis stage. Thus, LF index was useful for prediction of fibrosis in CHC patients regardless of steatosis. Because LF index of each activity grade and steatosis grade did not differ from each other, estimation of liver fibrosis by LF index demonstrated higher reproducibility than transient elastography.

In previously reports, diagnostic accuracy of liver fibrosis using RTE was inferior to transient elastography;[28] however, other studies have reported contrasting results.[19] The reason for this variability is probably because RTE technology and the equations used to calculate tissue elasticity are rapidly changing. The utility of elastic ratio, another RTE method for evaluation of liver fibrosis, was reported.[20] The elastic ratio is the ratio between the tissue compressibility of the liver and that of the intrahepatic small vessel. The AUROC of elastic ratio for predicting advanced fibrosis was 0.94 and was superior to LF index. Further, ARFI and real-time shear wave elastography were reported to have a high diagnostic accuracy of liver fibrosis.[10,11,29] There are currently no studies that directly compare LF index and those methods for diagnostic value of liver fibrosis. Therefore, further studies are needed to fully explore the potential of RTE, especially with regard to LF index.

Our study had several limitations. The number of patients with advanced fibrosis was small. The potential of LF index to differentiate patients with F3 and F4 needs to be explored with a large number of patients. Further, validation study is needed to evaluate the diagnostic accuracy of fibrosis stage, especially in comparison with other modalities.

In conclusion, LF index calculated by RTE is useful for predicting liver fibrosis, and diagnostic accuracy of LF index is superior to that of serum fibrosis markers.

Table 4 Diagnostic performance of LF index and serum fibrosis markers

	F0–2 vs F3–4					F0–1 vs F2–4				
	AUROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
LF index	0.84	90.6	71.1	54.7	95.2	0.81	84.3	70.3	69.4	84.9
Platelets	0.82	87.5	66.3	50.0	93.2	0.73	80.4	59.4	61.2	79.2
FIB-4 index	0.80	71.9	81.9	60.5	88.3	0.79	54.9	90.6	82.3	71.6
APRI	0.76	87.5	61.4	46.7	92.7	0.78	64.7	85.9	78.6	75.3

APRI, aspartate aminotransferase/platelet ratio index; AUROC, area under the receiver–operator curve; NPV, negative predictive value; PPV, positive predictive value.

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Virtual Sonography for Novice Sonographers: Usefulness of SYNAPSE VINCENT® with Pre-Check Imaging of Tumor Location

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Key Words
SYNAPSE VINCENT® · Ultrasound beginners · Virtual sonography

Abstract
Purpose: To evaluate the usefulness of a virtual ultrasound (US) imaging device as a tool to assist novice sonographers. ***Materials and Methods:*** A prospective blinded pilot study was conducted involving patients with liver lesions. Two sonographers and 2 medical doctors with less than 5 years of experience performed US examinations. The time needed to detect liver lesions on US and the success rate for detecting liver lesions with and without using the virtual US imaging device SYNAPSE VINCENT® (Fujifilm Medical Co., Tokyo, Japan) before US examination were evaluated. ***Results:*** Thirty-two patients with the following 42 liver lesions were included: liver cyst (n = 24), hemangioma (n = 8), hepatocellular carcinoma (n = 6), and liver metastasis (n = 4). The maximal diameter of these lesions ranged from 0.3 to 1.5 cm (mean ± SD, 0.8 ± 0.4). The average time for detecting liver lesions on US was 47.8 s (range, 7–113) with VINCENT and 112.9 s (range, 14–313) without VINCENT before US examination. There were significant differences in the duration of US examination with and without VINCENT ($p = 0.0002$, Student's t test). The rates for accurately detecting liver lesions were 100 and 76.2% (16/21) in US beginners with and without VINCENT, respectively. Significantly higher detection rates were found in the US beginners who used VINCENT compared to those who did not use VINCENT ($p = 0.047$, Fisher's exact test). ***Conclusion:*** Before US examination, a reference with VINCENT could contribute to the successful detection of liver lesions and could be time-saving for US beginners.

Introduction

Multidetector CT has been in clinical use since the late 1990s, and 3D imaging technology has markedly advanced. At the beginning of its clinical application, CT image reconstruction focused on displaying organs in real time [1, 2]. Recently, 3D imaging analysis has diversified. The ease and speed of obtaining needed images from 3D volume data have become important for the treatment of liver tumors, especially radiofrequency ablation for hepatocellular carcinoma [3, 4]. Especially in the liver, diag-

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