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Points to be considered when Applying FibroScan S Probe for Children with Biliary Atresia

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Abbreviations

TE, transient elastography; BMI, body mass index; APRI, aspartate aminotransferase-to-platelet ratio index; IQR, interquartile range; LSM, liver stiffness measurement; ICC, intraclass correlation coefficient

Conflict of Interest

The authors declare no conflict of interests.

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ABSTRACT

Objectives: With the introduction of smaller probes (S1, S2), the use of transient elastography has been expanded to children. Accordingly, we aimed to address points of consideration in probe choice and interpretation of measured liver stiffness by applying and comparing FibroScan S and M probes in biliary atresia.

Methods: Using S1, S2, and M probes, three liver stiffness measurements, success rates, and interquartile ranges were obtained from 100 patients. Patients were assigned to two groups according to thoracic perimeter (≤ 45 cm vs. > 45 cm). In both groups, obtained values were compared and the relationship between liver stiffness measurement and aspartate aminotransferase-to-platelet ratio index was analyzed.

Results: In the small-thorax group, success rate was highest with the S1 probe and the intraclass correlation coefficient (ICC) was the highest for S1 vs. S2 (0.98), in comparison to S1 vs. M (0.69) and S2 vs. M (0.77). In the large-thorax group, ICC was the highest for S2 vs. M (0.88), compared to S1 vs. S2 (0.69) and S1 vs. M (0.51). In the small-thorax group correlations between aspartate aminotransferase-to-platelet ratio index and liver stiffness measurement were stronger for the S1 (0.65) and S2 (0.64) than M (0.49). In the large-thorax group, all probes showed good correlation, S1 (0.68), S2 (0.62), and M (0.62).

Conclusions: We recommend that the S1 probe is more appropriate for use in small children, especially those with a thorax perimeter of less than 45 cm. If no S probe is available, M probe may be acceptable in children whose thorax perimeter is greater than 45 cm.

Keywords: transient elastography, liver fibrosis, biliary atresia, children

INTRODUCTION

Transient elastography (TE) is known as a useful noninvasive tool for the evaluation of liver fibrosis or predicting esophageal/gastric varices in chronic liver disease, even in children (1, 2). The S probes (S1, S2) of FibroScan, a transient elastography, have developed for use in children or small adults with thin subcutaneous tissue, narrow intercostal spaces, and small livers. The use of these S probes for children appears to be appropriate, and some studies have assessed the feasibility of these probes in children (3, 4). Control values of TE for children (4.7 kPa ± 1.08) have also been introduced (4); however clinical data for small children are still lacking. Recently Goldschimidt et al. systematically analyzed technical issues for TE in children (5). Based on their study, we further analysed practical issues for TE in much younger and more severe patients than previous studies (4, 5). Biliary atresia, as a subject of study, was thought to be appropriate due to its rapid progression of liver fibrosis, even in infancy, and its wide spectrum of liver stiffness values. We applied S1, S2 and M probes in young biliary atresia patients in the attempt to provide guidelines for probe choice and interpretation of results.

METHODS

Study Population and Data Collection

From October 2010 to September 2012, 100 patients (mean age = 3.87 years) with biliary atresia were enrolled consecutively who had undergone Kasai hepatoportoenterostomy but had not received liver transplantation. TE was not performed for the patients who are suffering acute cholangitis, hepatic failure, and significant ascites. Patients whose thoracic perimeter is larger than 75cm were excluded, because we were to evaluate the characteristics of pediatric patients with small body size. Patients' height, weight, and thoracic perimeter were measured, and body mass index (BMI) was calculated. TE and laboratory tests, including complete blood cell count and aspartate aminotransferase assessment, were performed on the same day. The aspartate aminotransferase-to-platelet ratio index (APRI), one of the validated noninvasive markers of liver fibrosis, was calculated and compared with the results of TE (6). This study protocol was approved by the Institutional Review Board of the Severance Hospital.

Transient Elastography

TE (FibroScan®, Echosens, Paris, France) was performed by one well-trained and experienced nurse who was not informed of patients' clinical data (7, 8). The M probe has a transducer with a diameter of 7 mm and can measure 35~75 mm depth of the liver, whereas the S1 and S2 probes have transducers of 5 mm diameter (to accommodate the narrow intercostal space of children) and are designed to measure 15~40 mm and 20~50 mm depth of the liver, respectively. The ultrasonic frequency of M probe is set in 3.5MHz, and those of S1 and S2 probe is set in 5MHz due to thinner tissue between skin and the liver parenchyma. The measurements were performed by placing a probe tip on the intercostal space at the area of right lobe of liver. Optimal target area was selected by ultrasound examination avoiding large vascular structures. TE measurements were conducted according to the manufacturer's recommendations without administrating sedative drugs. All patients were examined with the 3 types of probes even though the manufacturer had recommended a single suitable probe for the patient's thoracic perimeter (S1 probe for ≤ 45 cm, S2 probe for 45~75 cm and M probe for > 75 cm). Liver stiffness was measured repeatedly using the S1, S2, and M probes in each patient for obtaining more than 10 valid measurements per probe. Success rates (the ratio of valid shots to the total number of shots) with the probes were recorded and analyzed. For determining reproducibility of measurements, interquartile range (IQR)/median liver stiffness was recorded.

Statistical Analysis

Patients were divided into two groups based on their thoracic perimeter ($\leq$ 45 cm and > 45 cm). Thoracic perimeters were measured at the level of xiphoid process. Basic patient characteristics were compared using the T-test. Liver stiffness measurement (LSM), success rate, and interquartile range/liver stiffness measurement (IQR/LSM) of each probe in both groups were compared using a mixed model (post-hoc: Bonferroni correction). Intraclass correlation coefficient (ICC) analyses were performed to evaluate the reliability of LSM between different probes in each patient group. A Bland-Altman plot was drawn to determine the reproducibility and reliability of measurements. Correlations between LSMs obtained using each probe and the patients' APRI were analyzed. All statistical analyses were performed using SPSS software (version 18.0, SPSS Inc., Chicago, IL). A p value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Among the 100 patients, 26 were assigned to the small thoracic perimeter group ($\leq$ 45 cm) and 74 were assigned to the large thoracic perimeter group (> 45 cm). Characteristics of the study population are listed in Table 1. Age, height, weight, and BMI differed among the groups ($p < 0.05$), but APRI and LSM did not.

Comparison of Success Rates among Probes

Success rates of TE with each probe were recorded in both groups (Fig. 1A). Success rates of the S1, S2, and M probes were 96.9% ± 4.4%, 93.6% ± 6.7%, and 91.0% ± 9.2%, respectively, in patients with small thoracic perimeter; the corresponding values were 99.3% ± 2.7%, 96.8% ± 5.9%, and 97.0% ± 5.0%, respectively, in patients with large thoracic perimeter. The success rate of the S1 probe was significantly higher than that of the M probe in the small thoracic perimeter group ($p < 0.01$).

Comparison of IQR/LSM among Probes

The IQR/LSM ratios with the S1, S2, and M probes were calculated to assess the reliability of the test. The results were 0.23 ± 0.15, 0.20 ± 0.13, and 0.26 ± 0.16, respectively, in the small thoracic perimeter group and 0.17 ± 0.10, 0.14 ± 0.09, and 0.17 ± 0.09, respectively, in the large thoracic perimeter group. The mean IQR/LSM was larger in the small thoracic perimeter group (Fig. 1B).

Correlation of Measured Liver Stiffness between Probes: S1 versus S2, S1 versus M, and S2 versus M.

ICC was used to evaluate the correlation of LSM among the various probes (Table 2). In the small thoracic perimeter group, the ICC of S1 vs.S2 was highest (0.98). In the large thoracic perimeter group, the ICC of S2 vs. M was highest (0.88). Regardless of thoracic perimeter, the ICC of LSM obtained using every probe showed more than moderate correlation (ICC > 0.50). On the Bland-Altman plot, most points were within two standard deviations, thus demonstrating fair consonance between results with the two probes. However, some outliers were noted in cases with large mean LSM (Fig. 2). On a simple scatter plot, S probe seems to show large LSM compared with the M probe (Fig. 3). According to the linear mixed model, LSMs (mean ± SD) of the S1, S2, and M probes were 20.6 ± 17.9 kPa, 15.4 ± 12.8 kPa, and 12.3 ± 9.8 kPa, respectively; significant differences were observed among probes: S1 vs. S2 ($p < 0.001$), S1 vs. M ($p < 0.001$), and S2 vs. M ($p = 0.003$). Fig. 4 shows distributions of LSM values according to the probe with box and whisker plots.

Analysis of Correlation between APRI and LSM

In the small thoracic perimeter group, the correlation coefficient of APRI and LSM measured with the S1 and S2 probes was 0.65 and 0.64, respectively. However, the correlation coefficient of APRI and LSM measured with M probe in this group showed a relatively low value of 0.49. In contrast, in the large thoracic perimeter group, the correlation of APRI and LSM was good with all probes (S1 = 0.68, S2 = 0.63, and M = 0.62) (Table 3).

DISCUSSION

Determination of the degree of fibrosis in a chronically diseased liver is valuable because it provides physicians the ability to predict the development of liver-related complications. Although histopathologic examination of the liver is regarded as the gold standard for assessing liver fibrosis (9), the invasiveness of the test seriously limits its application. In particular, repeated examinations on serial follow up, especially in infants and children, are nearly impossible. In contrast, TE, a physical (ultrasonographic) method for evaluating fibrosis, is simple and noninvasive (10), and has been analyzed in many adults and some pediatric studies (2,3,11,12). Due to its noninvasiveness, TE has already been widely use in children, despite a lack of clinical data. For more valid application, studies on normal values have been conducted: One recent study of a healthy Chinese population revealed different normal LSM values, according to gender and age (13). Also, Engelmann et al. reported age dependent reference values for LSM in children (4.40-5.10 kPa) that showed high stiffness in older children (4).

In this study, we attempted to outline some practical issues when measuring TE in small patients. To highlight the impact of small body size, biliary atresia patients of a much younger age than those in previous studies (9.11 and 10.7 vs. 3.87 years) were enrolled (2, 3). Furthermore, to our knowledge, this is the first direct comparison of S1, S2, and M probes.

All probes used in both of our thoracic perimeter groups had success rates of more than 90%. This high rate might reflect the skill of our operator, who was well trained and has performed more than 15,000 TE examinations (7, 8). The success rate was higher in the large thoracic perimeter group, which probably illustrates the difficulty of measuring LSM in smaller children. We also found that in children with a small thoracic perimeter, the success rate of the S1 probe was significantly higher than that of the M probe, thus illustrating that the smaller probe is advantageous for the examination of small children. The IQR/LSM, the index of reliability and reproducibility (14, 15), was higher in children with small thoracic perimeter than in those with large thoracic perimeter. These findings suggest that TE has some limitations in small children. Although there were no statistically significant differences, the IQR/LSM of the S1 and S2 probes were lower than those of the M probe in children with small thoracic perimeter, further illustrating the advantage of using the S probes for small patients. When obtaining LSM in children, irritability or motion can hamper repeated measurement of the same area of the liver, and relatively small structures can make it difficult to identify just the parenchyma of the liver. Furthermore, narrow intercostal space may interrupt the propagation of the elastic shear wave (4). In the small thoracic perimeter group, the S probes showed better correlation than the M probe with APRI, which is known to be correlates with the degree of liver fibrosis (6). Although we did not compare the probes with the gold standard, these findings support the usage of S probe for small children.

However, for routine application of the S probe, there are some issues that need to be clarified. In our study, LSM tended to decrease with increase in the size of the probes (S1 > S2 > M), as has been reported (16, 17). Some studies (5, 18) have regarded this phenomenon as "overestimation of the S probe", however it might reflect "underestimation of the M probe" on the basis of better correlation between S probe and APRI. We also found that the tendency towards differences in LSM among the probes used was larger in patients with high LSM, a result similar to that reported previously (17). Therefore, caution is needed when interpreting values measured by S probe and patients with high LSM values. Goldschmidt et al. (5) reported that measuring conditions such as feeding status or general anesthesia can influence the results of TE. For objective evaluation, standardization of measuring protocol is needed. There are limitations to this study. One is that we could not keep the same NPO time before measuring LSM in all patients. Furthermore, liver biopsy should have been performed for decisive comparison.

In conclusion, the S probe has distinct merits in its high success rate and good correlation with APRI, especially in small children. Therefore, we recommend the use of the S1 probe in patients whose thoracic perimeter is less than 45 cm, and if the S probe is not available, the M probe may be acceptable for use in pediatric patients whose thoracic perimeter is greater than 45 cm. Because of possible differences, LSM values measured with a different probe should not be compared directly. For using LSM as an objective indicator, further clarification of reference ranges or cut off values for each probe is needed.

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Figure and Table Legends

FIGURE 1. Success rates (A) and IQR/LSM ratios (B) of S1, S2, and M probes in the large thoracic perimeter group and the small thoracic perimeter group. *Success rate of the S1 probe was significantly higher than that of the M probe in the small thoracic perimeter group (p = 0.0016). The IQR/LSM ratio among probes in both groups was not significantly different. Data are expressed as mean ± standard deviation.

FIGURE 2. Bland-Altman plot of the difference in LSM by two different probes versus the mean of LSM. The solid lines indicate mean difference, and dotted lines represent two standard deviations between two probes (A) S1 and S2; 5.2 ± 16.8 kPa, (B) S1 and M; 8.3 ± 22.3 kPa and (C) S2 and M; 3.0 ± 11.8 kPa. Outliers are noted inpatients with high mean LSM.

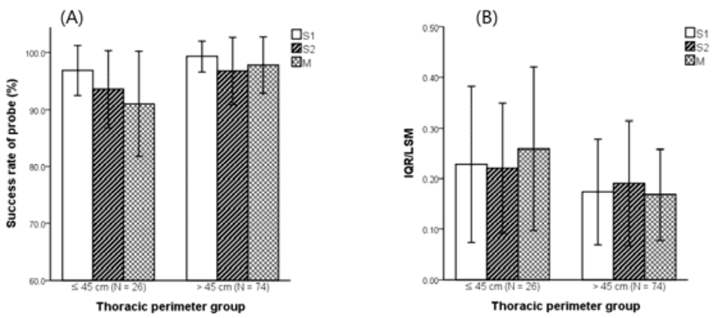
FIGURE 3. Correlations among LSMs determined using various probes. (A) S1 and M, (B) S2 and M. LSM determined using S1 and S2 probes was higher than determined using the M probe.

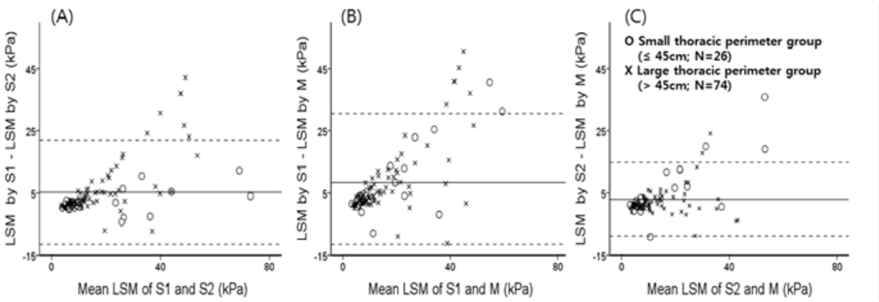
FIGURE 4. Box and whisker plot of LSM showing distributions of LSM according to the probe. The box represents the interquartile range, and the line in the box shows the median value. The whiskers indicate the highest and lowest values, and the circles represent outliers.

TABLE 1. Characteristics of the study population

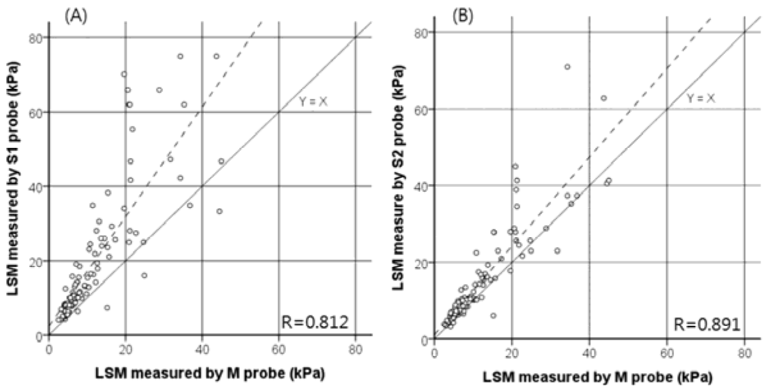
TABLE 2. Intraclass correlation coefficient (ICC) between probes

TABLE 3. Correlation between APRI and LSM by each probe


(A)
Success rate of probe (%)
100.0
90.0
80.0
70.0
60.0
S1
S2
M
≤ 45 cm (N = 26)
> 45 cm (N = 74)
Thoracic perimeter group
(B)
IQR/LSM
0.50
0.40
0.30
0.20
0.10
0.00
S1
S2
M
≤ 45 cm (N = 26)
> 45 cm (N = 74)
Thoracic perimeter group



(A)
LSM by S1 - LSM by S2 (kPa)
Mean LSM of S1 and S2 (kPa)
(B)
LSM by S1 - LSM by M (kPa)
Mean LSM of S1 and M (kPa)
(C)
O Small thoracic perimeter group
(≤ 45cm; N=26)
X Large thoracic perimeter group
(> 45cm; N=74)
LSM by S2 - LSM by M (kPa)
Mean LSM of S2 and M (kPa)


(A)
LSM measured by S1 probe (kPa)
LSM measured by M probe (kPa)
Y = X
R=0.812
(B)
LSM measure by S2 probe (kPa)
LSM measured by M probe (kPa)
Y = X
R=0.891

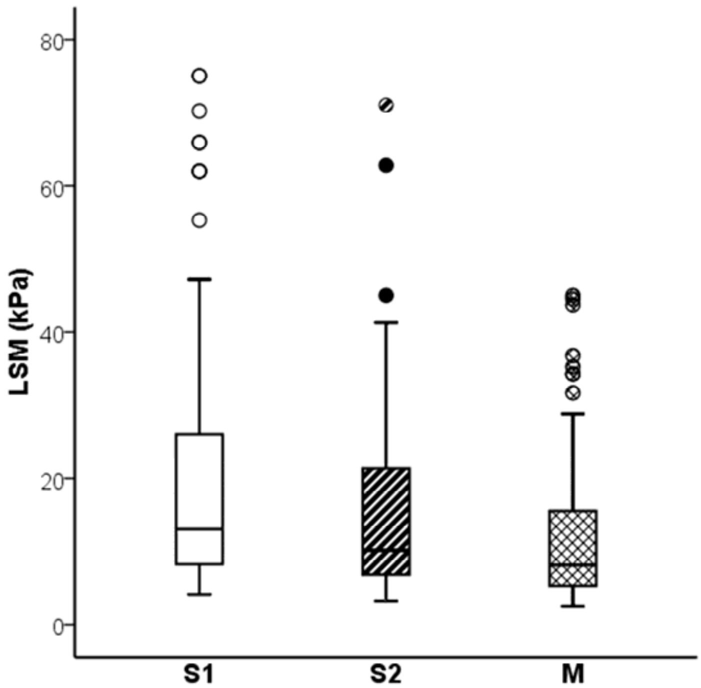

80
60
40
20
0
LSM (kPa)
S1
S2
M

TABLE 1. Characteristics of the study population

Parameter	Total patients (N = 100)	Thoracic perimeter ≤ 45 cm (N = 26)	Thoracic perimeter > 45 cm (N = 74)	*p*
Gender, M:F	38:62	11:15	27:47	NS
Age (range), year	3.9 ± 3.3	0.4 ± 0.3 (0.2-1.4)	5.7 ± 2.8 (1.0-13.6)	< 0.001
Thoracic perimeter, cm	54.0 ± 10.0	40.0 ± 3.1	58.9 ± 6.1	< 0.001
Height, cm	97.4 ± 28.3	60.4 ± 10.6	110.4 ± 19.6	< 0.001
Weight, Kg	17.4 ± 10.3	7.7 ± 11.4	20.8 ± 7.4	< 0.001
BMI	16.27 ± 2.23	15.10 ± 2.30	16.70 ± 2.10	0.003
Direct bilirubin, mg/dL	0.9 ± 1.0	1.8 ± 1.3	0.5 ± 0.6	< 0.001
Albumin, g/dL	3.9 ± 0.6	3.4 ± 0.5	4.0 ± 0.6	< 0.001
APRI	2.04 ± 1.71	2.19 ± 2.12	1.99 ± 1.56	0.624
LSM by S1 probe, kPa	20.6 ± 17.9	19.5 ± 20.0	21.1 ± 17.2	0.712
LSM by S2 probe, kPa	15.4 ± 12.8	17.3 ± 18.1	14.4 ± 10.1	0.440
LSM by M probe, kPa	12.3 ± 9.8	12.0 ± 11.2	12.5 ± 9.8	0.874

BMI, body mass index; APRI, aspartate aminotransferase-to-platelet ratio index; LSM, liver stiffness measurement

TABLE 2. Intraclass correlation coefficient (ICC) between probes

	ICC (95% confidence interval) of LSM measured by each probe		
	S1 and S2	S1 and M	S2 and M
Total (N = 100)	0.80 (0.72–0.86)	0.56 (0.41–0.68)	0.83 (0.76–0.88)
≤ 45 cm (N = 26)	0.98 (0.95–0.99)	0.69 (0.42–0.85)	0.77 (0.55–0.89)
> 45 cm (N = 74)	0.69 (0.55–0.79)	0.51 (0.32–0.66)	0.88 (0.82–0.92)

LSM, liver stiffness measurement

TABLE 3. Correlation between APRI and LSM by each probe

	≤ 45 cm (N = 26)			> 45 cm (N = 74)		
	LSM by S1	LSM by S2	LSM by M	LSM by S1	LSM by S2	LSM by M
R	0.65	0.64	0.49	0.68	0.63	0.62
p	< 0.001	< 0.001	0.011	< 0.001	< 0.001	< 0.001

APRI, aspartate aminotransferase-to-platelet ratio index; LSM, liver stiffness measurement; R, correlation coefficient