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Feasibility of non-enhanced CT for assessing longitudinal changes in hepatic steatosis

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Abstract

To evaluate the feasibility of computed tomography (CT) in the assessment of the change in hepatic steatosis (HS) in longitudinal follow-up by employing pathological HS as the reference standard.

We retrospectively evaluated 38 living liver donor candidates (27 men and 11 women; mean age, 29.5 years) who underwent liver biopsy twice and had liver CT scans within 1 week of each biopsy. Four readers independently calculated CT_{L-S} index by subtracting spleen attenuation from liver attenuation on non-enhanced CT images. The changes in pathological HS (ΔHS) and CT_{L-S} (ΔCT_{L-S}) between the 1st and 2nd examinations were assessed. The correlation between ΔHS and ΔCT_{L-S} was assessed using the linear regression analysis. Inter-observer measurement error for ΔCT_{L-S} among the 4 readers was assessed using the repeatability coefficient.

ΔCT_{L-S} showed a significant correlation with ΔHS in all readers ($r = 0.571-0.65$, $P < .001$). The inter-observer measurement error for ΔCT_{L-S} was ± 8.9. The ΔCT_{L-S} values beyond the measurement error were associated with a consistent change in HS in 83.3% (13/15) to 100% (15/15), with sensitivities of 47.8 to 79.9% and specificities of 86.7 to 100% for detecting an absolute change of $\geq 10\%$ in HS among the 4 readers. However, ΔCT_{L-S} values within the measurement error were associated with a consistent change in HS in 43.5% (8/19) to 61.5% (16/26).

The change in CT_{L-S} roughly reflects the change in HS during longitudinal follow-up. A small change in CT_{L-S} should not be considered meaningful, while a larger change in CT_{L-S} beyond the measurement error strongly indicates a true change in HS.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CT = computed tomography, HS = hepatic steatosis, HSI = hepatic steatosis index, HU = Hounsfield unit, ICC = intraclass correlation coefficient, MR = magnetic resonance, ROI = region-of-interest, US = ultrasonography.

Keywords: computed tomography, hepatic steatosis, liver

1. Introduction

Hepatic steatosis (HS) is a common abnormality occurring in approximately 30% of the general population in the United States,[1] and its clinical importance is being increasingly recognized. The HS is a component of nonalcoholic fatty liver disease, which may progress to steatohepatitis, fibrosis, and even cirrhosis in some patients.[2,3] The HS is associated with insulin resistance and is regarded as a hepatic manifestation of metabolic syndrome[4] also it is a critical in liver transplantation. Donor livers with HS are known to adversely affect the prognosis of liver transplantation recipients.[5]

Liver biopsy has been regarded as the standard method for HS assessment. However, this technique is invasive and, thus, is not suitable for screening a large number of subjects at risk and during follow-up examination of patients with HS. Therefore, noninvasive imaging techniques have been used to assess HS in clinical practice and research, and in particular, magnetic resonance (MR) spectroscopy and chemical-shift MR imaging are currently considered the most accurate imaging techniques.[6,7]

Computed tomography (CT) facilitates HS assessment in a quantitative manner using CT indices based on the measurement of liver attenuation. Although CT is not accurate in diagnosing mild HS,[7] it enables the diagnosis of moderate to severe HS with a high specificity.[6,8,9] Compared with MR spectroscopy and MR imaging, CT is more widely available and easier to perform. Thus, CT has been used to identify subjects with clinically significant HS for living liver donor evaluation[8,10–12] as well as in researches involving large-scale cohorts.[13–16] Furthermore, CT has also been utilized to assess the change in HS in longitudinal cohort studies[17] and

therapeutic clinical trials.[18,19] Although the performance of CT in diagnosing HS has been evaluated in a few studies,[7–11,20] no prior evaluation has been conducted on CT being a reliable technique for monitoring longitudinal change in HS.

Therefore, this study aimed to evaluate the feasibility of CT for assessing the change in HS during longitudinal follow-up by employing pathological HS as the reference standard.

2. Materials and methods

This study was approved by the institutional review board of Asan Medical Center. The requirement for informed consent was waived for this retrospective review.

2.1. Study population

From April 2001 to October 2016, a total of 6366 subjects underwent living liver donor work-up at our institution. The inclusion criteria for hepatic donor evaluation were the absence of any documented liver disease, negative serologic findings for hepatitis B or C, and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels below 3 times of the upper normal limit. Routine living liver donor evaluation included laboratory blood tests, abdominal ultrasonography (US), abdominal CT, and US-guided percutaneous liver biopsy. For the actual liver donors, intraoperative liver biopsy was routinely performed before donor liver resection for the final confirmation of the suitability of donors' liver for liver transplantation. Among the donor candidates, we retrospectively searched for the subjects who fulfill the inclusion and exclusion criteria of this study. The inclusion criteria were subjects who underwent liver biopsy twice or more times, and those who underwent liver CT within 1 week of each liver biopsy. The exclusion criteria were excess alcohol consumption, liver disease other than HS, and unavailable non-enhanced CT images. Thirty-eight living liver donor candidates (27 men and 11 women; mean age, 29.5 years; age range, 18–52 years) who met these criteria were included in this study. All subjects underwent liver biopsy twice within a mean time interval of 580.9 ± 926.7 days (range, 16–3963 days). The mean time interval between liver biopsy and CT was 0.9 ± 1.8 days (range, 0–7 days); 48 (63.2%) of 76 CT scans were performed on the same day of liver biopsy. The initial liver biopsy was performed by ultrasound-guided liver biopsy in all 38 subjects. The 2nd liver biopsy was performed either by US-guided liver biopsy (n=21) or by intraoperative wedge resection biopsy (n=17) which was routinely performed during donor hepatectomy in our institution. For 21 donors who underwent US-guided liver biopsy twice, liver biopsy was repeated for the follow-up examination of significant hepatic steatosis detected at the initial biopsy, which precludes liver donation in 18 subjects. The remaining 3 subjects did not donate liver at the time of initial biopsy because of the recipients' refusal to surgery, and then, 2048–3963 days after the initial donor work-up, the subjects were re-enrolled for donor evaluation.

2.2. CT examinations

Because of a long study period, various scanners and scan techniques were employed for CT examinations. The CT scans were performed using 16- (Sensation 16 [n=37], Siemens, Erlangen, Germany; and Lightspeed 16 [n=17], GE Medical System, Milwaukee, Wis) or 64- (Definition [n=22], Siemens) multidetector row CT scanners. Non-enhanced images were obtained by employing a beam collimation of 16×1.5 mm (Sensation 16), 8×2.5 mm (Lightspeed 16), or 24×1.2 mm (Definition); a spiral pitch of 1 (Sensation 16 and Definition) or 1.35 (Lightspeed 16); a tube voltage of 100 (n=13) or 120 (n=63) kVp; and a tube current of 150 mAs (Lightspeed 16) or of a variable mA (Sensation 16 and Definition) with an automatic exposure control (Care Dose 4D; Siemens; a maximum effective dose of 200 mA). Images were reconstructed at a section thickness of 5 mm and at an interval of 5 mm.

Four readers, including one of the abdominal radiology faculty members (Reader-1, with 12 years of experience in abdominal radiology), 1 abdominal imaging fellow (Reader-2), and 2 medical school students (Reader-3 and -4, in the 2nd and 3rd year of medical college, respectively) independently performed quantitative analysis of non-enhanced CT images. The CT images were anonymized and randomized for review. All readers were blinded to the results of liver biopsy and those of the CT analysis conducted by other readers. Hepatic attenuation was measured by averaging Hounsfield unit (HU) values of 8 1.5-cm^2 circular regions-of-interest (ROIs): 2 ROIs were placed at 2 different sites in each segment of the right hepatic lobe (hepatic segments V, VI, VII, and VIII according to the Couinaud system). Splenic attenuation was obtained by averaging HU values of 3 1.5-cm^2 circular ROIs placed in the upper, middle, and lower thirds of the spleen (Fig. 1). For both hepatic and splenic attenuation measurements, ROIs were placed under special care so as to exclude macroscopic vessels. Before performing image review, the 2 medical school students studied the cross-sectional anatomy of the liver using web contents (https://www.imaios.com/en/e-Anatomy) and were trained under the supervision of a senior radiologist (S.S.L.) for the placement of ROIs in the liver and the spleen in 5 example cases which are not included in this study. CT_{L-S} was used as the CT index for assessing HS in this study and was calculated by subtracting the mean HU value of the spleen from that of the liver.[20] The change in CT_{L-S} between the 1st and the 2nd CT scan (ΔCT_{L-S}) was calculated as CT_{L-S} on the 2nd CT minus CT_{L-S} on the 1st CT.

2.3. Liver biopsy

All liver biopsies were performed as a part of routine living liver donor evaluation at our institution. The US-guided percutaneous liver biopsy was performed using an 18-gauge needle (Stericut 18G coaxial; TSK Laboratory, Tochigi, Japan). Two or more biopsy specimens, with each section measuring approximately 1.5 cm in length, were obtained at 2 different sites from the right hepatic lobe. Intraoperative liver biopsy was performed by wedge resection at the time of donor liver resection. Approximately $1 \times 1 \times 1$ cm samples of liver tissues were obtained from sites deeper than 1 cm from the liver surface at both right and left hepatic lobes. Hematoxylin–eosin and Masson trichrome stains were used to stain biopsy specimens. The degree of HS was visually assessed using a percentage scale, i.e., the amount of liver parenchyma replaced by steatotic droplets. The HS was graded as none (<5%), mild (5%–29%), moderate (30%–59%), or severe (≥60%). The change in HS between the 1st and 2nd biopsies (ΔHS) was calculated by subtracting HS (%) estimated during the 1st biopsy from the HS (%) estimated during the 2nd biopsy. For the analysis of the diagnostic performance of ΔCT_{L-S} in detecting ≥5% ΔHS and ≥10% ΔHS, the study population was divided into 2 sets of subgroups, i.e. those with significant change in HS
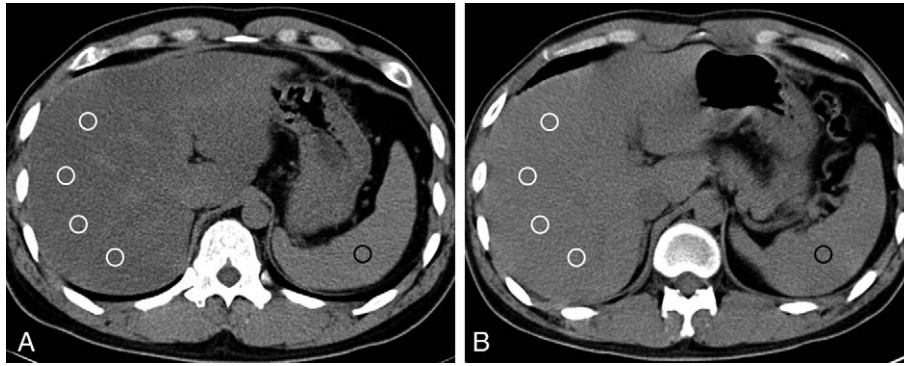
Figure 1. Non-enhanced axial CT images of a 30-year old male living liver donor candidate. A and B, 4 1.5-cm circular ROIs (white circles) were placed in the hepatic segments VIII and VII that is devoid of macroscopic vessels. A 1.5-cm circular ROI was positioned in the spleen (black circle). The values obtained by the readers 1, 2, 3, and 4 after subtracting spleen attenuation from liver attenuation (CT_{L-S}) measurements were −21.5, −23.8, −22.7, and −21.9 at the 1st CT scan (A) and 4.4, 2.1, 2.9, and 3.4, respectively, at the 2nd CT scan (B). Liver biopsy revealed moderate hepatic steatosis (60%) at the time of the 1st CT scan (A) and mild hepatic steatosis (25%) at the time of the 2nd CT scan (B).

and those without significant change in HS, using the threshold ΔHS values of 5 and 10%.

2.4. Clinical information

The body weight, height, and laboratory data, such as the levels of serum AST, ALT, and total bilirubin, obtained within 1 week prior to each biopsy were recorded. The mean time interval between liver biopsy and laboratory tests was 1.3 ± 1.9 days (range, 0–7 days) with 56.6% (43/76) of laboratory data obtained on the same day of liver biopsy. Body mass index (BMI) was calculated as weight (kg) divided by the squared value of height (m^2). As the clinical indices for predicting hepatic steatosis, AST–ALT ratio was calculated by dividing serum AST (IU/L) with ALT (IU/L) value, and hepatic steatosis index (HSI) was calculated as reported previously[21]; HSI = 8·AST–ALT ratio + BMI (+2 if DM; 2+ if female). The changes in BMI (ΔBMI), AST–ALT ratio (ΔAST–ALT ratio), and HSI (ΔHSI) were assessed as the difference value calculated by subtracting the values at the time of the 1st liver biopsy from those at the time of the 2nd liver biopsy.

2.5. Statistical analysis

The clinical and histologic features at the initial and the 2nd liver biopsy were compared using the paired *t* test or Fisher's exact test. The correlation of ΔHS with $ΔCT_{L-S}$ and clinical indices (ΔBMI, ΔAST-ALT ratio, ΔHSI) were evaluated using the linear regression analysis. The correlation coefficients for $ΔCT_{L-S}$ were compared with those for the clinical indices using the z-test. Interobserver agreement among the readers with regard to the measurement of $ΔCT_{L-S}$ values and CT_{L-S} values on the 1st CT scan was evaluated using the intraclass correlation coefficient (ICC). The ICCs of $ΔCT_{L-S}$ were compared with those of CT_{L-S}, and the ICC of $ΔCT_{L-S}$ measured by the 2 radiologists was compared with the ICC of $ΔCT_{L-S}$ measured by the 2 medical students using the z-test. Interobserver measurement error ranges among the 4 readers in the measurement of $ΔCT_{L-S}$ and CT_{L-S} values were evaluated using repeatability coefficient.[22] The interobserver measurement error range was used as the threshold for $ΔCT_{L-S}$ while calculating the sensitivity, specificity, and accuracy of $ΔCT_{L-S}$ in detecting ≥5% ΔHS and ≥10% ΔHS.

Statistical analysis was performed using SPSS statistics v.22 software (IBM, New York, NY) and MedCalc software (MedCalc Software, Mariakierke, Belgium). A *P* value of < .05 was considered to indicate a statistically significant difference.

3. Results

3.1. Characteristics of study population

The clinical and histological characteristics of the study population are summarized in Table 1. At the time of the 1st liver biopsy, the mean degree of HS was $22.6 \pm 22.7\%$, and 18 subjects (47.3%) had moderate to severe HS. The degree of HS significantly decreased at the 2nd liver biopsy ($7.4 \pm 8.3\%$, $P < .001$), with moderate hepatic steatosis being present only in 1 (2.6%) subject. There was also a significant decrease in BMI ($P = .011$), AST ($P = .02$), ALT ($P = .003$), total bilirubin ($P = .018$), HSI ($P = .001$), and CT_{L-S} ($P < .001$) at the time of 2nd liver biopsy compared with the values at the 1st biopsy.

3.2. Changes in hepatic steatosis, CT index, and clinical indices

Between the 1st and the 2nd liver biopsy, the change in HS ranged from −65 to 30%. Seven subjects had no HS at both 1st and 2nd biopsy (ΔHS = 0%); the 2nd biopsy in these subjects were performed by means of an intraoperative wedge resection biopsy during a donor hepatectomy. Twenty-four subjects had a decreased HS at the 2nd biopsy compared with the 1st biopsy, with ΔHS ranging from −1 to −65%, while nine subjects showed an increased HS with ΔHS of 1 to 30%. The ΔHS had a significant inverse correlation with $ΔCT_{L-S}$ for all 4 readers ($r = 0.65, 0.57, 0.63,$ and 0.62 for readers 1, 2, 3, and 4, respectively; $P < .001$), with the regression coefficients of −1.64, −1.47, −1.61, and −1.51, respectively, for readers 1, 2, 3, and 4 (Fig. 2), which indicates that the ΔHS decreases by 1.47 to 1.64% for each unit value increase in $ΔCT_{L-S}$. The Δ HS also showed significant correlations with ΔBMI ($r = 0.46, P = .004$), ΔAST-ALT ratio ($r = 0.41, P = .01$), and ΔHSI ($r = 0.59, P < .001$). The correlation coefficients for $ΔCT_{L-S}$ were slightly higher than those for ΔBMI ($P = .242–.522$), ΔAST-ALT ratio ($P = .155–.372$), and ΔHSI ($P = .660–.930$) without any statistically significant difference.

Table 1

Characteristics of study population.

	At 1st liver biopsy	At 2nd liver biopsy	*P* value
Age, y	29.5 ± 9.9 (18–52)		
Sex (male:female)	27:11		
Body mass index (kg/m^2)	24.9 ± 3.1 (18.9–31.5)	24.1 ± 2.5 (18.7–29.2)	.011
Hepatic steatosis (%)	22.6 ± 22.7% (0–80%)	7.4 ± 8.3% (0–30%)	.000
Hepatic steatosis (grade)			.003
None (<5%)	15 (39.5%)	17 (44.7%)	
Mild (5%–29%)	5 (13.1%)	20 (52.6%)	
Moderate (30%–59%)	14 (36.8%)	1 (2.6%)	
Severe (≥60%)	4 (10.5%)	0 (0%)	
AST (IU/L)	24.3 ± 10.1 (14–61)	20.1 ± 4.9 (12–33)	.020
ALT (IU/L)	29.9 ± 19.3 (6–94)	19.68 ± 7.8 (6–40)	.003
Total bilirubin (mg/dL)	0.987 ± 0.455 (0.4–2.9)	0.837 ± 0.418 (0.2–1.9)	.018
AST-ALT ratio	0.974 ± 0.401 (0.53–2.50)	1.107 ± 0.306 (0.74–2.17)	.075
HSI[*]	34.7 ± 4.8 (23.6–43.8)	32.3 ± 3.6 (24.8–42.1)	.001
CT$_{L-S}$[†]	−0.047 ± 9.4 (−22.7, 15.8)	7.8 ± 5.8 (−4.7, 20.5)	<.001

Values are expressed as mean ± standard deviation (range) or as the number of subjects (%). AST = aspartate aminotransferase, ALT = alanine aminotransferase, APRI = aspartate aminotransferase to platelet ratio index, HSI = hepatic steatosis index.

[*] HSI = 8·AST-ALT ratio + BMI (+2 if DM; 2+ if female).

[†] Calculated by subtracting spleen attenuation values from liver attenuation values on non-enhanced CT.

3.3. Interobserver agreement of CT index measurements

The ICC for the ΔCT_{L-S} measurements taken by the 4 readers was 0.89 (95% confidence interval [CI], 0.82–0.93), which was significantly lower than the ICC (0.96; 95% CI, 0.92–0.98]) for CT_{L-S} measurements taken on the 1st CT scans ($P = .023$). The ICC for ΔCT_{L-S} measured by 2 radiologists (0.95; 95% CI, 0.91–0.97) did not significantly differ from the ICC for ΔCT_{L-S} measured by 2 medical students (0.91; 95% CI, 0.83–0.95; $P = .0215$). The interobserver measurement error range among the 4 readers, represented by the repeatability coefficients, was 8.9 (95% CI, 7.9–10.2) for ΔCT_{L-S} and 6.7 (95% CI, 5.9–7.7) for CT_{L-S} on the 1st CT scans.

3.4. Detection of change in CT$_{L-S}$ using CT index

In 7 subjects with no absolute change in HS between 2 biopsies ($\Delta HS = 0\%$), ΔCT_{L-S} for 4 readers ranged from −9.2 to 11.6. As shown in Fig. 2 and Table 2, the ΔCT_{L-S} beyond the interobserver measurement error range (i.e., $\Delta CT_{L-S} > 8.9$ or < -8.9) was more frequently associated with a change in HS that is consistent with the change in CT_{L-S} (i.e., a decrease in HS in cases of positive ΔCT_{L-S} or vice versa) than the ΔCT_{L-S} within the interobserver measurement error range, with statistically significant differences noted for the values measured by the readers 1 ($P = .012$) and 4 ($P < .001$). Moreover, changes in HS consistent with the changes
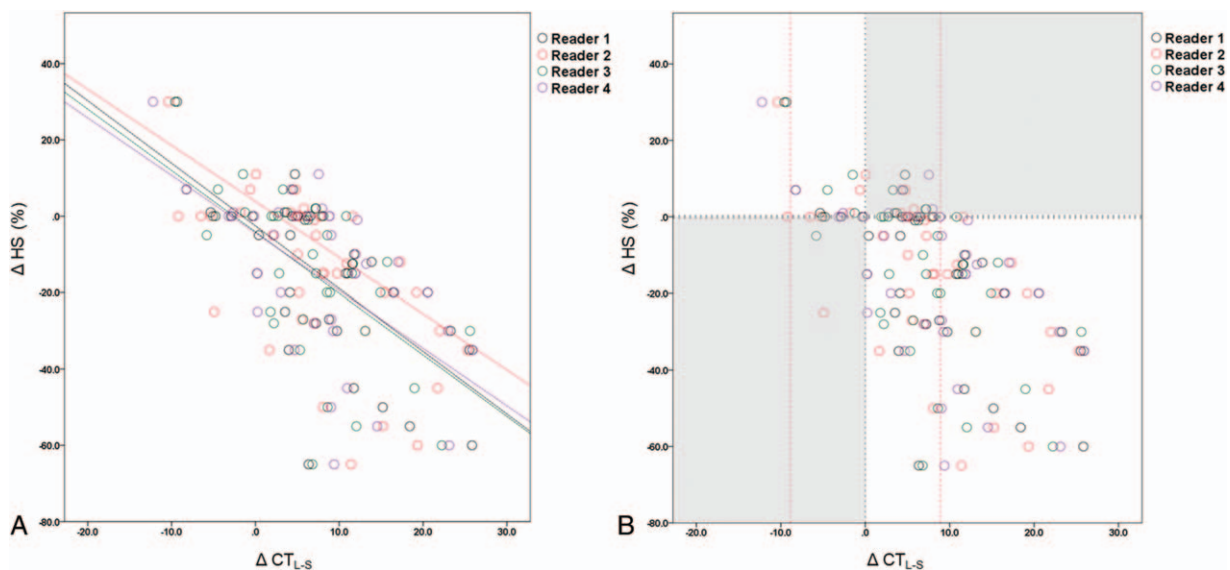

Figure 2. Scatter plots for the change in hepatic steatosis (ΔHS) according to the change in CT$_{L-S}$ value (ΔCT$_{L-S}$) measured by 4 readers. A and B, the circles indicate data points measured by the 4 readers. The same scatter plot was presented with the regression lines for the values measured by the 4 readers (A) or with reference lines (B). A, the oblique dotted lines were the regression lines. B, the vertical red dotted lines indicate the interobserver measurement error range of ΔCT$_{L-S}$ (−8.9–8.9). The horizontal grey dotted line indicates no change in hepatic steatosis between the 1st and the 2nd biopsies (ΔHS = 0%). The grey-colored right upper and left lower quadrants of the scatter plot indicate a change in hepatic steatosis, which is inconsistent with the change in ΔCT$_{L-S}$. Note that most data points in the horizontal grey dotted line and grey-colored quadrants are within the interobserver measurement error range of ΔCT$_{L-S}$.

The change in hepatic steatosis according to the magnitude of change in CT index.

Readers	Change in HS	Change in CT_{L-S}		P value
		$-8.9 < \Delta CT_{L-S} \leq 8.9$	$\Delta CT_{L-S} > 8.9$ or < -8.9	
Reader 1	Consistent change*	13 (56.5%)	15 (100%)	.012
	No change	7 (30.4%)	0 (0%)	
	Inconsistent change†	3 (13.0%)	0 (0%)	
Reader 2	Consistent change*	13 (56.5%)	13 (86.7%)	.09
	No change	5 (21.7%)	2 (13.3%)	
	Inconsistent change†	5 (21.7%)	0 (0%)	
Reader 3	Consistent change*	16 (61.5%)	11 (91.7%)	.145
	No change	6 (23.1%)	1 (8.3%)	
	Inconsistent change†	4 (15.4%)	0 (0%)	
Reader 4	Consistent change*	8 (43.5%)	19 (100%)	<.001
	No change	7 (36.8%)	0 (0%)	
	Inconsistent change†	4 (21.1%)	0 (0%)	

$\Delta CT_{L-S} = CT_{L-S}$ value at the time of the 2nd biopsy minus CT_{L-S} value at the time of the 1st biopsy, $CT_{L-S} =$ liver attenuation minus spleen attenuation, HS = hepatic steatosis.
* Consistent change refers to the change in hepatic steatosis in a direction consistent with the change in ΔCT_{L-S}, e.g., decrease in HS in positive ΔCT_{L-S} cases.
† Inconsistent change refers to the change in hepatic steatosis in a direction opposite to the change in ΔCT_{L-S}, e.g., increase in HS in positive ΔCT_{L-S} cases.

in CT_{L-S} were noted in 83.3% (13/15) to 100% (15/15) for the ΔCT_{L-S} beyond the interobserver measurement error range (Fig. 1) but were observed only in 43.5% (8/19) to 61.5% (16/26) for the ΔCT_{L-S} within the interobserver measurement error range.

When the interobserver measurement error range was used as the threshold value to indicate a meaningful change in HS (i.e., $\Delta CT_{L-S} > 8.9$ or < -8.9), the sensitivity and specificity for detecting an absolute change of $\geq 5\%$ in HS were in the range of 40.7 to 66.7% and 77.8 to 100%, respectively, and the sensitivity and specificity for detecting an absolute change $\geq 10\%$ in HS ranged from 47.8 to 79.9% and from 86.7 to 100%, respectively (Table 3).

4. Discussion

Our study evaluated the feasibility of CT for assessing the change in HS by using the pathologic degree of HS as the reference standard. As the quantitative CT index, we used CT_{L-S} in this study because this index is best validated for its accuracy[7,8,11,20] and normal reference range[20] among CT indices.

The performance of ΔCT_{L-S} beyond measurement error range in the detection of the change in hepatic steatosis.

	Diagnostic performance of ΔCT_{L-S}	
	$\geq 5\%$ change in HS	$\geq 10\%$ change in HS
Reader 1		
Sensitivity (%)	55.6 (15/27)	65.2 (15/23)
Specificity (%)	100 (9/9)	100 (15/15)
Reader 2		
Sensitivity (%)	48.2 (13/27)	56.5 (13/23)
Specificity (%)	77.8 (7/9)	86.7 (13/15)
Reader 3		
Sensitivity (%)	40.7 (11/27)	47.8 (11/23)
Specificity (%)	88.9 (8/9)	93.3 (14/15)
Reader 4		
Sensitivity (%)	66.7 (18/27)	79.9 (17/23)
Specificity (%)	88.9 (8/9)	86.7 (13/15)

Numbers in parentheses are the number of subjects, which are used to calculate the percentages. The diagnostic performance was calculated using the cut-off ΔCT_{L-S} value of ± 8.9. HS = hepatic steatosis.

Our study demonstrated a statistically significant correlation between ΔCT_{L-S} and ΔHS, indicating that it is feasible to use the change in CT_{L-S} value for assessing the change in HS during longitudinal follow-up. However, our results also indicated that the actual clinical utility of ΔCT_{L-S} in the follow-up of patients with HS may be limited because of the following reasons. First, the correlation between ΔCT_{L-S} and ΔHS in our study was not very strong, with correlation coefficients ranging from 0.571 to 0.65 among the 4 readers. The change in clinical indices also showed a significant correlation with ΔHS, although their correlation coefficients were slightly lower than the correlation coefficients between ΔCT_{L-S} and ΔHS. Second, ΔCT_{L-S} measurements appear to be subject to a considerable measurement error. A wide range of ΔCT_{L-S} (-9.21–11.6) was noted even in patients with no HS during both the 1st and 2nd biopsy. Interobserver agreement with regard to the measurement of ΔCT_{L-S} was poorer than that associated with the measurement of CT_{L-S}. Given these findings, we considered that a small change in ΔCT_{L-S} during a longitudinal follow-up assessment should not be considered meaningful. Therefore, we used the interobserver repeatability coefficient (i.e., ± 8.9) as the threshold for a meaningful change in CT_{L-S} beyond measurement error. In our study, the ΔCT_{L-S} beyond this threshold could detect a $\geq 5\%$ or $\geq 10\%$ change in HS, with a high specificity but a low to moderate sensitivity. Our findings, taken together, suggest that CT is not a reliable method for the longitudinal follow-up assessment of HS, but the change in CT_{L-S} beyond the measurement error range strongly indicates the true change in HS. Considering its low accuracy, potential hazard of ionizing radiation, and cost, performing CT examination in clinical practice for longitudinal follow-up assessment of HS would not be justified. Clinical indices less costly than CT, such as BMI, AST-ALT ratio, and HSI may be used as cost-effective alternatives to CT, since these indices showed significant correlations with the change in HS in our study. For clinical or research conditions where precise determination of the change in HS is critical, non-invasive imaging examinations with well-established diagnostic performance, such as MR spectroscopy or MR imaging,[6,7] would be preferred.

The measurement error of a quantitative imaging index should be determined in a repeatability condition in which a test is repeated within a short time interval to avoid true biologic changes in tested subjects.[22] However, due to the risk of ionizing radiation, repeatedly performing CT scans over a short period is

not practical in a research setting. Therefore, we considered the estimation of interobserver repeatability coefficient to be a more practical method to address the measurement error range of ΔCT_{L-S} in our study.

In our study, 2 abdominal radiologists and 2 medical school students were involved in the image review. The ICCs for the interobserver agreement of ΔCT_{L-S} were slightly stronger between the 2 radiologists than between the 2 students, but the difference was not statistically significant. Furthermore, the correlation coefficients between ΔCT_{L-S} and ΔHS were similar among the 4 readers. This finding indicates that CT_{L-S} measurement does not require much experience and can be relatively easily performed by readers with limited experience. We believe that the results obtained from readers with varying experience in this study facilitate generalization of our findings.

Our study has some limitations. First, our study involved multiple CT scanners and various scanning parameters. Given a significant influence of CT type/manufacturer on the measured liver attenuation in a previous study,[9] the measurement error range of ΔCT_{L-S} revealed in our study may have been over-estimated compared with the range obtained under typical conditions of measurement repeatability assessment. Second, the sample size in our study is relatively small. However, subjecting people with no liver abnormality, other than HS, to liver biopsy and CT multiple times is not recommended in clinical practice and will not be ethical for research. Therefore, despite the small size of study population, we believe that our study provides useful and valuable information regarding the feasibility and limitations of CT for the follow-up assessment of HS. Third, liver biopsy which served as the reference standard for HS assessment in our study may be subject to some degree of sampling error. Finally, our study was a retrospective study and, thus, is subject to selection bias.

In conclusion, the change in CT_{L-S} roughly reflects the change in HS during longitudinal follow-up. A small change in CT_{L-S} should not be considered meaningful because it may occur even without an actual change in HS. A larger change in CT_{L-S} beyond the measurement error range (± 8.9) strongly indicates the true change in HS.

Author contributions

Conceptualization: Seung Soo Lee.
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