

## Original article

# Usefulness of contrast-enhanced computed tomography for diagnosing hepatic steatosis

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**Background:** The diagnosis of hepatic steatosis has been well-described on unenhanced computed tomography (UECT) study. However, current UECT often discarded from the abdominal CT protocol due to radiation dose reduction.

**Objective:** To determine accuracy of contrast-enhanced CT (CECT) for diagnosis of hepatic steatosis.

**Methods:** A total of 1,001 patients who underwent unenhanced and portal venous phase abdominal CT studies were assessed by using region-of-interests of liver and spleen, and visual detection of focal fat sparing. UECT diagnostic criteria were used as the standard reference.

**Results:** The optimal cut-offs on CECT images were 110 Hounsfield unit (HU) of liver attenuation and -20 HU of liver-splenic differential (L-S) attenuation. Sensitivity, specificity, accuracy and receiver operating characteristic curve areas for quantitative liver attenuation values were 90.4%, 73.6%, 75.9% and 0.926, respectively; and for L-S attenuation values were 83.1%, 70.8%, 72.5% and 0.856, respectively. Qualitatively, geographic fat sparing was 100.0% specificity; however, its sensitivity (50.7%) was rather low.

**Conclusion:** Portal venous phase CECT can be used for detection of hepatic steatosis in abdominal CECT study without the preceding unenhanced phase.

**Keywords:** Hepatic steatosis, fatty liver, contrast-enhanced computed tomography, focal fat sparing.

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Hepatic steatosis or fatty liver disease has become a common health problem with an estimated prevalence of 10.0–58.0% in the general population.<sup>(1)</sup> It is a reversible condition that can progress to steatohepatitis and eventually cirrhosis in some patients.<sup>(1)</sup> Superimposed hepatic steatosis has an effect on disease progression and treatment response in viral hepatitis patients as well as that related to worsened recipient prognosis after liver transplantation.<sup>(2)</sup>

Liver biopsy with histologic analysis is a gold standard for assessment of hepatic steatosis. However, because of the invasiveness, the use of this procedure potentially declines and is replaced by cross-sectional imaging techniques included

ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) which are non-invasive, cost-effectiveness and high accurate in the detection of the steatotic liver.<sup>(3-5)</sup> Ultrasound is the first imaging modality due to its availability and low-cost technique, but its use is somewhat limited due to qualitative assessment, unable to detection of low level of steatosis and inaccuracy in obese patients.<sup>(3)</sup> CT and MRI provide better accuracy and good reproducibility; however, CT is less expensive and is more widely used than MRI.<sup>(3)</sup>

Unenhanced CT (UECT) that is a simplified and non-invasive diagnostic method has widely been used to evaluate hepatic steatosis without the need for liver biopsy proven. Whereas contrast-enhanced CT (CECT) is still a questionable role and tends to be less useful.<sup>(4)</sup> Although the prior studies proposed about diagnostic criteria that had quite high accuracy, none of them was used in routine clinical practice.<sup>(1, 4-5)</sup>

To date, many abdominal CECT studies are potentially performed without the preceding UECT to avoid unnecessary radiation exposure. Meanwhile,

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the CECT diagnostic criteria of hepatic steatosis are inconclusive. Therefore, the purpose of this study was to determine accuracy of the optimal cut-off on CECT for detecting hepatic steatosis and to analyze CT factors that might affect the accuracy.

### Materials and methods

The retrospective analysis was based on patient data searching from the picture archiving and communication system (PACS) at our hospital. A total of 2,483 consecutive patients who underwent unenhanced and portal venous phase CECT of the upper abdomen on the same day between January 2014 and August 2014 were enrolled. The patients who had the following criteria were excluded: liver cirrhosis, acute hepatic injury, numerous hepatic space-taking lesions, liver attenuation on UECT reached 75 Hounsfield unit (HU),<sup>(6)</sup> previous right hepatectomy, biliary ductal dilation, asplenia or splenectomy, presence of artifacts related to metallic materials or motion, presence of more than trace ascites and incomplete patient information. A final 1,001 patients were recruited in our study. The Institutional Review Board's approval was obtained for the retrospective study. The informed consent of the subject was waived.

All patients were performed at least UECT and portal venous-phase CECT images of the upper abdomen by using a 64-multidetector CT scanner (Discovery CT750 HD; GE healthcare, UK) after 6-hour fasting with the following parameters: beam collimation, 64 x 0.625 mm; beam pitch, 1.375; gantry rotation time, 0.5 sec; 120 kVp; the maximum allowable tube current set at 200 mAs on an automated dose reduction system (Auto or Smart mA, GE Healthcare); field of view to fit.

Depending on the patients' sizes and CT protocols, estimated volume of contrast administration was individually used about 2 mL/kg in most of abdominal CT protocols, not exceeding 100 - 120 mL/dose; and 2 - 3 mL/kg in pancreatic protocol or CT angiography because of higher injection rate, not exceeding 120 - 150 mL/dose. Therefore, a bolus of 100 to 120 mL of Iopromide (Ultravist 300; Bayer Schering Pharma AG, Berlin, Germany) or Iohexol (Omnipaque 350; GE Healthcare) was intravenously injected at a rate of 1.2 to 4.0 mL/s through 20 or 22-gauge angiographic catheter inserted into an antecubital vein in each patient. Portal venous-phase images were obtained in the range of 70 to 100 seconds after the initiation of intravenous contrast administration. Axial images with 2.5-mm slice thickness were

reconstructed for both UECT and portal venous-phase CECT images.

For each individual, liver and splenic attenuations were measured in HU by averaging two  $1.0 \pm 0.1$ -cm<sup>2</sup> circular region-of-interests (ROIs) placed above and below the main portal vein plane in both UECT and CECT images on the same/resemble slices by illustrating vascular anatomy. To prevent partial-volume averaging effect, special care was taken to avoid measurements of vessels, focal lesions, areas of artifact and the edge of organ. Furthermore, the posterior half of right hepatic lobe was only assessed due to similar anatomic location and artifacts between the liver and spleen (Figure 1). For each CT-phase image, ROIs of the liver and splenic measurements were calculated separately in mean attenuation values. Liver-splenic differential (L-S) attenuation were then computed.

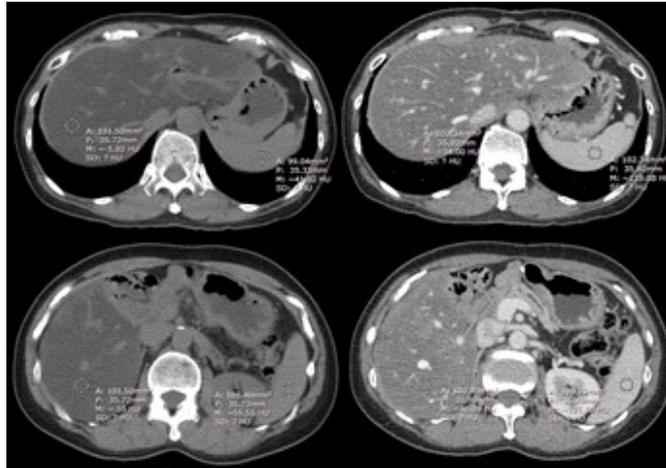
Typical characteristics of focal fat sparing including a geographic area of relatively increased attenuation in the liver, locations in specific areas (e.g. adjacent to falciform ligament, ligamentum venosum, porta hepatis and gallbladder fossa) and absence of a mass effect on vessels and other liver structures<sup>(1, 7)</sup> (Figure 2) on CECT images were recorded.

Either the liver attenuation on UECT image of less than or equal to 40 HU<sup>(7)</sup> or L-S attenuation less than or equal to -10 HU<sup>(8)</sup> was used as the reference standard for diagnosis of moderate to severe hepatic steatosis. Biopsy proof was omitted.

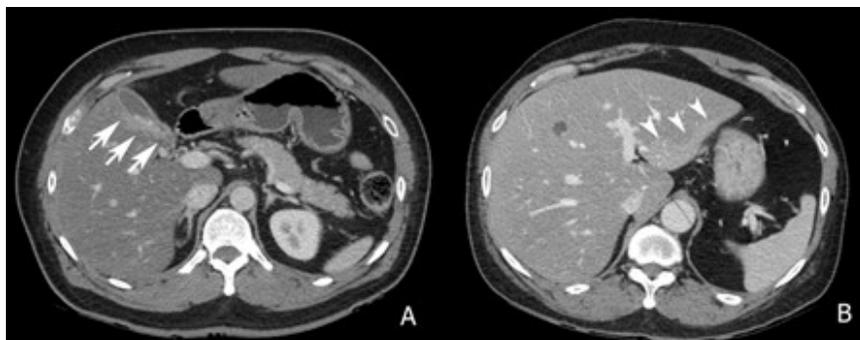
All drawn ROIs and identified focal fat sparing were performed by a 3<sup>rd</sup>-year radiology resident (T.T.) on a PACS system (Synapse, Fuji Medical Systems) by using standard adjustable abdominal window width and level settings. In order to analyze interobserver agreement, 52 patients were randomly selected, and the ROI measurements and focal fat sparing detection were redone by a board-certificated radiologist (T.C. with over 3 years of experience in abdominal imaging) who did not know the initial results.

### Statistical analysis

Statistical analysis was performed using SPSS 17.0 for Windows (SPSS, Chicago, IL). Normally distributed continuous data are presented as mean  $\pm$  standard deviation (SD), 95% confidence interval (CI). Non-parametric data are presented as numbers of cases and percentages. Comparing hepatic attenuation and L-S attenuation between steatotic and non-steatotic groups were analyzed by unpaired Student's *t* - test.



**Figure 1.** Attenuation measurements of liver and spleen on UECT (left) and portal venous-phase CECT (right) in two levels. Four liver ROIs were drawn above and below plane of portal vein bifurcation avoiding vessels, bile ducts, focal lesions and liver edge. Two splenic ROIs were drawn in the same manner and CT slice. 91 x 64 mm (300 x 300 DPI).



**Figure 2.** Presence of focal fat sparing in the liver on CECT images. (A): A geographic fat sparing was detected nearby gallbladder fossa (arrow). (B): Focal fat sparing located adjacent to ligamentum venosum and along subcapsular region of hepatic segment III (arrowhead). Aortic dissection and hepatic cyst were noted. 118 x 46 mm(300 x 300 DPI)

The optimal threshold for diagnosis of hepatic steatosis on CECT was determined by Receiver Operator Characteristic (ROC) curve and calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy over a range of possible liver attenuation diagnostic threshold, L-S attenuation diagnostic threshold or combined. The maximum overall accuracy value was chosen. Presence of focal fat sparing was also evaluated efficacy by calculating sensitivity, specificity, PPV, NPV and accuracy.

The effect of delayed CT scan time, rate of contrast injection, volume and concentration of contrast media on the liver and splenic enhancements (the attenuation differences between CECT and UECT images) was analyzed by Pearson correlation.

Interobserver agreement was determined by using paired *t*-test and Cohen's Kappa ( $\kappa$ ) statistics. The scale of the Cohen's Kappa used for interpretation of weighted *k* statistics was: slight agreement 0 - 0.20; fair agreement 0.21 - 0.40; moderate agreement 0.41 - 0.60; substantial agreement 0.61 - 0.80; and almost perfect agreement 0.81 - 1.00. *P* - value < 0.05 was considered to be a statistical significance.

## Results

A total of 1,001 patients (mean age, 58.1 years; range, 18 - 90 years), including 419 males (mean age, 59.9 years; range, 21 - 88 years) and 582 females (mean age, 56.8 years; range, 18 - 90 years), constituted the study population. The clinical indications for the examinations were mainly

abdominal pain (29.0%) and patients with cancers as follows: colorectal cancer (24.0%), breast cancer (8.5%), gastrointestinal stromal tumor (5.4%), lymphoma (4.7%), lung cancer (3.3%) and pancreatic cancer (3.3%).

Using the UECT diagnostic criteria, 136 (13.6%) of 1,001 patients had hepatic steatosis (mean age,  $56.9 \pm 11.8$  years). Of these, 44.1% were male. The values of the liver and L-S attenuation on both UECT and CECT images as well as the presence of focal fat sparing are displayed in Table 1.

For the diagnosis of hepatic steatosis on CECT, the area under curves (AUCs) of the liver and L-S

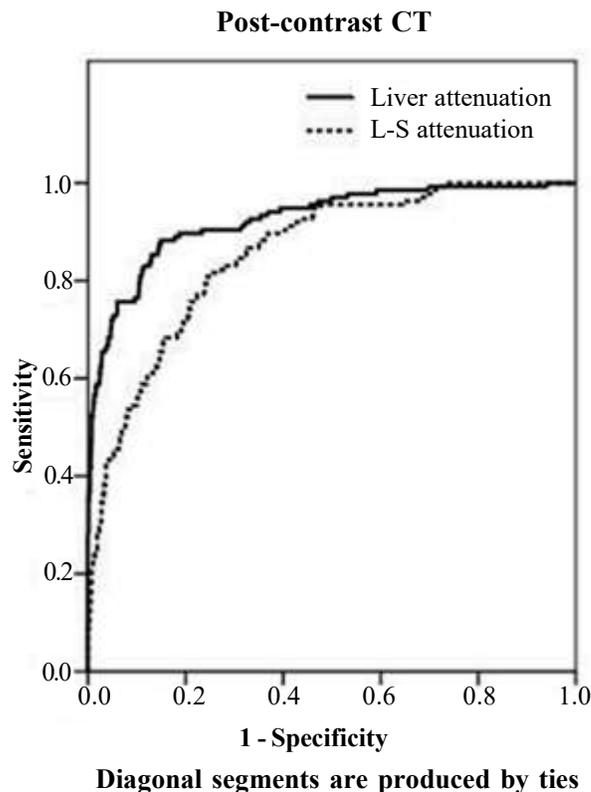
attenuations were calculated about 0.926 [95% CI, 0.900 – 0.952] and 0.856 [95% CI, 0.824 - 0.888], respectively (Figure 3). The optimal cut-offs of the liver and L-S attenuations which were the upper limit to diagnose hepatic steatosis were summarized along with corresponding sensitivity, specificity, PPV, NPV and accuracy in Table 3. The cut-offs were 110 HU for liver attenuation and -20 HU for L-S attenuation, using as the diagnostic criteria. The sensitivity, specificity, PPV, and accuracy of the such criteria are described in Table 2.

**Table 1.** Attenuation values and presence of focal fat sparing.

	With steatosis	Without steatosis	P-value
<b>UECT (Mean±SD; HU)</b>			
Liver attenuation	30.8 (±11.3)	57.9 (±6.5)	<0.001*
L-S attenuation	-17.5 (±11.4)	8.3 (±6.4)	<0.001*
<b>CECT (Mean±SD; HU)</b>			
Liver attenuation	82.8 (±21.6)	122.0 (±17.8)	<0.001*
L-S attenuation	-43.9 (±23.9)	-12.6 (±18.0)	<0.001*
Focal fat sparing (%)	69 (50.7)	0 (0)	<0.001*

SD = standard deviation, HU = Hounsfield unit.

\*P - value less than 0.05 was statistically significant.



**Figure 3.** The ROC curve showed the diagnostic performance of liver and L-S attenuations on CECT for the diagnosis of hepatic steatosis. 78 x 85 mm (300 x 300 DPI)

**Table 2.** Diagnostic performance of the attenuation values on contrast-enhanced CT for diagnosing hepatic steatosis.

		Liver attenuation	L-S attenuation	Combination of two criteria
Cut-off value*		110	-20	
Sensitivity**	Value	90.4(123/136)	83.1 (113/136)	77.2(105/136)
	95% CI	83.9-94.6	75.5-88.7	69.1-83.8
Specificity**	Value	73.6(637/865)	70.8(613/865)	88.2(613/865)
	95% CI	70.5-76.5	75.5-88.8	85.8-90.2
PPV**	Value	35.0(123/351)	30.9(113/365)	50.7(105/207)
	95% CI	32.1-38.1	26.3-36.0	43.7-57.7
NPV**	Value	98.0(637/650)	96.4(613/636)	96.1(763/794)
	95% CI	96.5-98.9	94.5-97.6	94.4-97.3
Accuracy**	Value	75.9(760/1001)	72.5(726/1001)	86.7(868/1001)

\*Values less than or equal to the cutoff value (HU) indicate a positive diagnosis of fatty liver.

\*\*Data are presented as percentages. Data in parentheses are the number of subjects used to calculate the percentage.

Sixty-nine (50.7%) of the 136 steatotic patients had focal fat sparing; none of the finding was detected in non-steatotic patients. The sensitivity, specificity, PPV, NPV and accuracy of the presence of focal fat sparing were 50.7%, 100.0%, 100.0%, 92.8% and 93.3%, respectively.

Only the delayed scan time showed mild negative correlation with splenic enhancement ( $r = -0.207$ ,  $P < 0.001$ ), whereas the injected rate, volume and concentration of contrast media did not. Regarding the liver enhancement, liver and splenic attenuations, and L-S attenuation, they each had no correlation with

delayed CT scan time and all parameters of contrast administration (Table 3).

The subjects for analyzing interobserver agreement consisted of 18 males (mean age, 59.9 years) and 34 females (mean age, 58.9 years). The measurement values between two readers showed no significant difference of all quantitative parameters. There was substantial agreement in detection of focal fat sparing between the two readers ( $\kappa = 0.729$ ; [95% CI, 0.571-0.835],  $P < 0.001$ ). The diagnosis of hepatic steatosis had 100.0% interobserver agreement.

**Table 3.** Correlation of each parenachymal enhancement with CT scan time and parameters of contrast administration.

	Delayed CT scan time	Contrast administration		
		Injection rate	Volume	Concentration
Liver enhancement	$r=0.007$ $P=0.819$	$r=0.104$ $P=0.001^*$	$r=0.043$ $P=0.171$	$r=0.060$ $P=0.059$
Splenic enhancement	$r=-0.207$ $P<0.001^*$	$r=-0.162$ $P<0.001^*$	$r=0.063$ $P=0.045^*$	$r=0.039$ $P=0.215$
Liver attenuation	$r=-0.011$ $P=0.738$	$r=0.042$ $P=0.188$	$r=-0.021$ $P=0.514$	$r=0.024$ $P=0.439$
Splenic attenuation	$r=-0.192$ $P<0.001^*$	$r=-0.155$ $P<0.001^*$	$r=0.052$ $P=0.097$	$r=0.041$ $P=0.195$
L-S attenuation	$r=0.179$ $P<0.001^*$	$r=0.197$ $P<0.001^*$	$r=-0.074$ $P=0.020^*$	$r=-0.015$ $P=0.637$

$r$  = correlation coefficient,  $P = P$  - value

\* $P$  - value less than 0.05 was statistically significant

## Discussion

The UECT has traditionally been utilized for the non-invasive diagnosis of moderate to severe hepatic steatosis with high specificity without the need for biopsy proven. Several prior studies have confirmed that the UECT had high accuracy and reliability.<sup>(5,8-11)</sup> In our study, the diagnostic criteria on the UECT was defined as liver attenuation less than or equal to 40 HU or L-S attenuation of 10 HU, at the least.<sup>(7,9)</sup>

Recently, many abdominal CT studies are potentially omitted UECT for radiation reduction. As a result, the assessment of hepatic steatosis might be affected. Previous literatures have proposed new diagnostic criteria of hepatic steatosis on CECT images with variable indices and accuracies.<sup>(1,4,7-9,12-15)</sup> In our study, we reevaluated portal venous-phase CECT criteria in the diagnosis of hepatic steatosis, showing high accurate diagnosis when quantitative measurement including the liver attenuation or L-S attenuation was used. Although some prior authors were interested and studied the L-S attenuation as a parameter for prediction of the hepatic steatosis,<sup>(4,8,12)</sup> our study, surprisingly, demonstrated that the accuracy of liver attenuation alone was higher than that of L-S attenuation.

Furthermore, we found that the liver attenuation discriminatory threshold of 110 HU which had a sensitivity of 90.4%, a specificity of 73.6% and an accuracy of 75.9% was loose agreement with the previously reported.<sup>(4,13)</sup> Monjardim RF, *et al.*<sup>(13)</sup> have reported that a 104-HU cut-off extended from the formula of Kim DY, *et al.*<sup>(4)</sup> was utilized as a diagnostic criterion with 100.0% sensitivity and 36.0% specificity, revealing higher sensitivity but less specificity than our results. These differences might be a strong influence of the selection bias towards patients with mild degree of steatosis from the lesser threshold of the standard reference in the Monjardim's study.<sup>(13)</sup> The L-S attenuation discriminatory threshold of -20 HU also had high sensitivity, specificity and accuracy, being similar to the previous studies.<sup>(4,12)</sup> Jacob JE, *et al.*<sup>(12)</sup> have described that the L-S attenuation of -20.5 HU afforded the highest overall diagnostic sensitivity and specificity when CECT was obtained delayed scan time at 80 - 100 sec. The delayed scan time in Jacob's study<sup>(11)</sup> and our study were overlapped and seem to be a similar range. Kim DY, *et al.*<sup>(4)</sup> have found that an optimal threshold for diagnosing 30.0% hepatic stenosis might be the L-S

attenuation of -19 HU with 69.2% sensitivity and 95.8% specificity. Additionally, we created a further method using a combination of the two diagnostic criteria which became the most specificity rate than each criterion separately did. Despite having higher accuracy, the combined criteria affected a substantial decrease in sensitivity. Therefore, we supposed to discuss the usefulness of the CECT criteria into 2 clinical scenarios depending on treatment planning. Firstly, we need to initiate non-invasive treatment such as lifestyle modification as soon as possible in this setting, a higher-sensitivity criterion by using the liver attenuation or L-S attenuation threshold might be practical. While, if we would realize a need for liver biopsy, the most-specificity, combined criteria should be chosen to avoid an unnecessary tissue proven.

Discovery of focal fat sparing on CECT could be useful for the diagnosis of hepatic steatosis with 50.7% sensitivity and 100.0% specificity, similar to the previous publish.<sup>(1)</sup> Lawrence DA, *et al.*<sup>(1)</sup> have shown 62.0% sensitivity and 100.0% specificity by using focal fat sparing.

In several studies,<sup>(8,12,14)</sup> the liver and splenic enhancements on the CECT were mainly affected by concentration of the contrast medium including volume, rate and timing of administration, and circulation. Johnston RJ, *et al.*<sup>(14)</sup> have established that contrast injection rate and CT scan time significantly influenced on the optimal L-S threshold and limited the clinical usefulness as well. The publication of Johnston RJ, *et al.*<sup>(14)</sup> was supported by subsequent studies.<sup>(8,12)</sup> Our study, in contrast to the others,<sup>(8,12,14)</sup> demonstrated that the contrast concentration and delayed scan time almost had no influence on parenchymal measurements except that the splenic enhancement had low inverse correlation with the delayed scan time ( $r = -0.207$ ,  $P < 0.001$ ). In clinical practice, all CT scan parameters are individually adjusted for providing truly portal venous phase, achieving good image quality and optimizing radiation dose, therefore, the effects of contrast concentration and imaging delayed time appear to be less influential as they are generally determined by the previous authors.<sup>(4,8,12,14)</sup>

Our study had some limitations, however. First, the retrospective design could lead to confounding bias. In order to avoid such bias, the large sample size was applied. Second, pathologic confirmation was omitted; previous literatures have confirmed that UECT had high accuracy and reliability for the

diagnosis in routine clinical practice.<sup>(1,6,8-11)</sup> Third, conditions related to hepatic iron deposition and hyperemia which can cause an increase of hepatic attenuation<sup>(16)</sup> and apparently focal fat sparing<sup>(1)</sup> were not considered. Finally, several uncontrolled factors such as habitus, body mass index, cardiac output and underlying disease<sup>(1)</sup> might influence on the parenchymal enhancement.

### Conclusion

We concluded that both quantitative and qualitative assessments on CECT were simple, non-invasive and highly accurate for diagnosing moderate to severe hepatic steatosis. Thus, portal venous-phase CECT might be an alternative application in detection of the steatotic liver.

### Conflict of interest

The authors, hereby, declare no conflict of interest.

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