Morphometric change of liver cirrhosis: etiological differences correlated with progression

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Aims and objectives

Liver cirrhosis is the end stage of a variety of chronic diffuse liver diseases, and is irreversibly progressive leading to hepatic dysfunction, portal hypertension and hepatocellular carcinoma. It is a major public health problem worldwide [1]. Therefore, to identify the causative factors and quantify the stage and/or activity of liver cirrhosis are important clinically. To achieve this, liver biopsy is most commonly used as the reference standard for assessing liver fibrosis. Although liver biopsy is a relatively safe procedure, there are various procedure-related risks such as intraabdominal bleeding, associated with a mortality rate of one in 10 000-12 000 [2, 3]. In addition, it also is subject to inherent risks that include interobserver variability and sampling errors [4].

Various kinds of morphometric changes are well known to occur in diffuse liver diseases, especially in liver cirrhosis, and they are important for the imaging diagnosis, estimation of severity, and understanding of the pathophysiology of the underlying etiologies. For the objective evaluation of these morphometric changes, conventional cross-sectional imaging by multi-detector computed tomography (MDCT) or magnetic resonance (MR) imaging is essential [5-14]. Furthermore, recent advances in MDCT have made it possible to obtain rapid volumetric scanning and three-dimensional reconstruction and provided a new method for precisely measuring liver volume and evaluating intrahepatic vascular structures [6, 7].

Morphometric changes of liver cirrhosis on imaging commonly include atrophy of the medial segment and right lobe and hypertrophy of the lateral segment and caudate lobe [6-14]. Although several reports have shown that the morphometric variations of hepatic segments in cirrhosis differ depending on the etiologies of cirrhosis [15], these reports focused mainly only on a part of a segment such as the caudate lobe and analyzed only virus-related or alcoholic cirrhosis, while most of them lumped together various etiologies [8-14]. In addition to differences related to the underlying etiology, morphometric changes may also depend on the progression of cirrhosis [5].

The purpose of this study was to evaluate the morphometric changes in liver cirrhosis using MDCT volumetry, and to analyze the differences in morphometric changes among different etiologies, namely virus-related, alcoholism, and NASH-related, and different stages of liver cirrhosis.
Methods and materials

Patients

Our study focused on virus-induced (hepatitis B or C), alcoholic, and NASH-related cirrhosis because of the high worldwide prevalence in of these conditions. Consecutive patients with cirrhosis due to alcoholism (n = 66) and NASH (n = 88) between October 2005 and December 2009, and 96 consecutive patients with cirrhosis due to hepatitis C or B virus infection between April 2008 and December 2009 who underwent upper abdominal dynamic CT at our institution were enrolled. All cases with cirrhosis were pathologically confirmed by percutaneous liver biopsy (Fig.1). Between January 2009 and December 2009, 54 age- and sex-matched patients with clinically diagnosed normal liver (no findings indicating liver disease or diabetes mellitus based on blood tests and imaging diagnosis within 3 months and patient history) who underwent dynamic CT were selected as a control group. The inclusion criteria for all patients were as follows: (a) older than 40 years; (b) space-occupying lesions in the liver smaller than 3 cm in diameter and less than 3 in number; (c) no history of surgical procedures including transarterial chemoembolization and/or radiofrequency ablation; (d) absence of the below-mentioned anatomic variations of the major intrahepatic portal veins; and (e) availability of good contrast images permitting automatic volumetric analyses. One hundred and seventy-two men and 78 women with a mean age of 66.1 years ± 10.1 (mean ± standard deviation) (range, 40-87) in the cirrhosis group, and 29 men and 25 women with a mean age of 62.4 years ± 7.6 (range, 41-75) in the control group were enrolled. In the cirrhosis group, 149 were classified as Child-Pugh class A, 57 as class B, and 44 as class C.

Definition of hepatic segments and anatomical exclusion criteria

In standard portal vein anatomy, the main portal vein typically divides at the hepatic hilus into the left and right portal veins. The left portal vein supplies the lateral segment and medial segment. The right portal vein divides into the right anterior trunk that supplies the anterior segment and the right posterior trunk that supplies the posterior segment [16]. The feeding branches into the caudate lobe directly arise from the main portal trunk, left and right portal vein, or posterior branch [17]. Patients with variations different from the above-mentioned most common portal anatomical patterns were excluded, because these anatomic variations may result in specific morphometric changes in cirrhosis, which could potentially bias the analysis.

Imaging Techniques

Abdominal dynamic CT images were obtained with a LightSpeed VCT 64 (GE Medical Systems, USA). Images were acquired through the liver in a craniocaudal direction with a 0.625 × 64 beam collimation. Other CT parameters were as follows: Auto mA (GE
Healthcare; 10-700 mA, Noise Index of 8.0); 120 kVp; detector collimation, 2.5 mm; table speed, 14 mm per rotation; gantry rotation time, 0.5 s; reconstruction section thickness of 2.5 mm and a reconstruction interval of 2.5 mm. Following precontrast CT, a dynamic contrast study was performed using the Smart Prep option (GE Medical Systems) and 600 mgI/kg of nonionic contrast material (iomeprol, Iomeron 350; Eisai, Tokyo, Japan) was administered for thirty seconds. The arterial phase scanning was initiated just after a 200 Hounsfield unit enhancement threshold was achieved in the aorta at the level of the celiac artery. The portal and equilibrium-phase scanning was performed at 35-second and 115-second delays, respectively, from the time of initiation of the arterial phase scanning.

**Body surface area (BSA) measurement**

BSA was calculated using Du Bois and Du Bois's formula (BSA = [0.0061 × BH (cm) + 0.0124 × BW (kg)]) \[18\] using body weight and body height recorded at the time of the CT examination to explore the possibility that the data might be modified by differences in this parameter.

**Volumetry of the entire liver and hepatic segments**

The volumes of the total liver, lateral, medial, anterior, and posterior segments, and the caudate lobe were measured in all patients; however, in the patients classified as Child-Pugh class C, discrimination between the anterior and posterior segments was difficult because of poorer visualization of intrahepatic portal veins, and only the volume of the right lobe was measured. All volumetric measurements were automatically performed using a method similar to that outlined in previous reports [6, 7, 19, 20] with a workstation (Virtual Place Lexus; AZE, Tokyo, Japan). In this method, the following steps were conducted as follows: first, the liver margins on the portal phase source images were defined using an algorithm for optimal boundary detection in real time; second, the portal veins on portal phase source images were segmented using a region-growing algorithm with automatically determined thresholds; third, portal veins were separated and analyzed; fourth, the vascular territories were automatically determined and volumetrically calculated based on individual portal branches [20]. Results of the determined area were presented using surface shaded display and volume-rendering techniques.

To allow for differences among individuals, total liver volume per BSA ratio was calculated [7]. The volume of the right lobe was calculated by the sum of the anterior and posterior segments except for in Child-Pugh class C. The proportion of each area relative to the total liver was calculated by dividing the volume of each hepatic area by the total liver volume.

**Statistical Analysis**
The distribution of sex in each Child-Pugh class in the three etiologies and control group was analyzed using the chi-square test, while the significance of differences in age, BSA, total liver volume, total liver volume per BSA, and each proportion was analyzed using the Kruskal-Wallis test. When a significant difference among groups was identified, multiple pairwise comparisons were performed using a Wilcoxon rank sum test with Bonferroni adjustments. As a secondary analysis, changes in total liver volume and total liver volume per BSA in each etiology in different stages of cirrhosis were also analyzed using the Kruskal-Wallis test. P values less than 0.05 were considered to indicate statistical significance. All analyses were performed with statistical software (Dr. SPSS II for Windows, version 11.0.1 J; SPSS, Chicago, Ill).
Images for this section:

**Pathological images of three different etiologies (Hematoxylin-Eosin staining)**

<table>
<thead>
<tr>
<th>Viral infection</th>
<th>Alcoholism</th>
<th>Nonalcoholic steatohepatitis</th>
</tr>
</thead>
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<td><img src="image4" alt="Image" /> × 10</td>
<td><img src="image5" alt="Image" /> × 10</td>
<td><img src="image6" alt="Image" /> × 10</td>
</tr>
</tbody>
</table>

**Fig. 1:** Pathological images of three different etiologies (Hematoxylin-Eosin staining)

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Results

Clinical features of the patients

Clinical features of the patients with liver cirrhosis classified according to the etiology and stage and patients without definite diffuse liver diseases (control group) were summarized in Figure 2. The patients with alcoholic cirrhosis showing Child-Pugh class A and B stage demonstrated a significantly higher proportion of males than females (p < 0.05). Neither age nor BSA distribution significantly differed among the patients with different etiologies in any Child-Pugh class or the control group (p > 0.05).

Total liver volume and total liver volume per BSA

Total liver volume and total liver volume per BSA were significantly larger in patients with alcoholic liver cirrhosis with Child-Pugh class A stage than in those with other etiologies and the control group (p < 0.001). On the other hand, no significant differences were observed among the three etiologies in Child-Pugh class B or C. Total liver volume and total liver volume per BSA significantly decreased with progression of cirrhosis in all patients with each etiology (p < 0.05) (Figs. 3 and 4).

The volume and volume ratio of each segment

The volume and volume ratio of each segment and the results of multiple pairwise comparisons among the patients with different etiologies in each Child-Pugh class and control group were summarized in Figure 5. Morphometric changes associated with all etiologies commonly included atrophy of the medial segment and right lobe and hypertrophy of the lateral segment and caudate lobe in Child-Pugh class A, B and C compared with control group (p < 0.05).

Multiple pairwise comparisons between each etiology

The results of the multiple pairwise comparisons between each etiology were summarized in Figs. 5, 7, and 9. In Child-Pugh class A patients, the proportion of lateral segment to the total liver in the patients with NASH was significantly smaller than that in the patients with virus-related (p < 0.001) or alcoholic cirrhosis (p < 0.001), the proportion of medial segment in the patients with NASH significantly larger than that in the patients with virus-related (p = 0.021) and alcoholic cirrhosis (p = 0.049), the proportion of anterior segment in the patients with NASH significantly larger than that in the patients with virus-related (p = 0.004) and alcoholic cirrhosis (p < 0.001), and the proportion of caudate lobe in the patients with virus-related cirrhosis significantly smaller than that in the patients with NASH (p < 0.001) and alcoholic liver cirrhosis (p < 0.001). In addition, the proportion of right lobe to the total liver was significantly larger in the patients with NASH than in the
patients with alcoholic liver cirrhosis ($p < 0.001$). There was no significant difference in the proportion of posterior segment to the total liver among the patients with the three different etiologies ($p > 0.05$) (Figs. 6 and 7). In Child-Pugh class B patients, the proportion of lateral segment to the total liver was significantly smaller in the patients with NASH than in those with alcoholic cirrhosis ($p < 0.001$), the proportion of medial segment significantly larger in the patients with NASH than in those with alcoholic cirrhosis ($p = 0.045$), the proportion of anterior segment significantly larger in the patients with NASH than in those with alcoholic cirrhosis ($p = 0.003$), and the proportion of caudate lobe significantly smaller in the patients with virus-related cirrhosis than in those with alcoholic liver cirrhosis ($p = 0.001$). The proportion of posterior segment and right lobe to the total liver did not differ significantly among the patients with the three different etiologies ($p > 0.05$) (Figs. 8 and 9). In Child-Pugh class C patients, the proportion of each segment to the total liver did not show significant differences among the patients with the three different etiologies ($p > 0.05$) (Figs. 10 and 11).
The data of age and BSA were expressed as means ± standard deviations. P value expressed the value between the control group and three etiologies in each Child-Pugh class. The patients with alcoholic cirrhosis showing Child-Pugh class A and B stage demonstrated a significantly higher proportion of males than females (p < 0.05). Neither age nor BSA distribution significantly differed among the patients with different etiologies in any Child-Pugh class or control group (p > 0.05).

**Fig. 2:** Clinical features of the patients

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Fig. 3: Total liver volume

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Total liver volume per body surface area among control group and three etiologies in each Child-Pugh class.

Fig. 4: Total liver volume per BSA

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### Table: Volume and volume ratio of each segment

<table>
<thead>
<tr>
<th>Segment</th>
<th>Child-Pugh class A</th>
<th>Child-Pugh class B</th>
<th>Child-Pugh class C</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Virus</td>
<td>Alcoholism</td>
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<tr>
<td>Number of patients</td>
<td>54</td>
<td>54</td>
<td>51</td>
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<td>Lateral segment</td>
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<td>Volume (mL)</td>
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<td>233.9±99.8</td>
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<td>Proportion (%)</td>
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<td>28.5±4.6</td>
<td>37.6±7.5</td>
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<td>P values</td>
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<td>Medial segment</td>
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<td></td>
<td></td>
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<tr>
<td>Volume (mL)</td>
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<td>132.9±47.7</td>
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<td>Proportion (%)</td>
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<td>11.7±2.6</td>
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<tr>
<td>P values</td>
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<td>Anterior segment</td>
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<td>Volume (mL)</td>
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<td>284.7±63.6</td>
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<td>Proportion (%)</td>
<td>35.9±3.8</td>
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<td>23.7±6.8</td>
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<tr>
<td>P values</td>
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<td>Posterior segment</td>
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<td>Volume (mL)</td>
<td>328.6±79.6</td>
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<td>Proportion (%)</td>
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<td>28.2±4.3</td>
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<td>P values</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Caudate lobe</td>
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<tr>
<td>Volume (mL)</td>
<td>63.3±14.6</td>
<td>111.6±36.8</td>
<td>184.6±66.3</td>
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<td>Proportion (%)</td>
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<td>9.3±2.4</td>
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<td>P values</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Right lobe</td>
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<tr>
<td>Volume (mL)</td>
<td>377.1±163.5</td>
<td>571.8±164.5</td>
<td>711.8±267.7</td>
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<tr>
<td>Proportion (%)</td>
<td>62.8±5.4</td>
<td>48.6±6.3</td>
<td>47.8±6.9</td>
</tr>
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<td>P values</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
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</table>

P value expressed the multiple pairwise comparisons between different etiologies in each Child-Pugh class and control group. Morphometric changes associated with all etiologies commonly showed atrophy of the medial segment and right lobe, and hypertrophy of the caudate lobe and lateral segment in Child-Pugh class A, B, and C compared with control group (p < 0.05).

**Fig. 5:** The volume and volume ratio of each segment

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Proportion of each segment to the total liver volume of three etiologies in Child-Pugh class A.

The proportion of lateral segment to the total liver was significantly smaller in the patients with NASH than in those with virus-related (p < 0.001) and alcoholic cirrhosis (p < 0.001), the proportion of medial segment significantly larger in the patients with NASH than in those with virus-related (p = 0.021) and alcoholic cirrhosis (p = 0.049), the proportion of anterior segment significantly larger in the patients with NASH than in those with virus-related (p = 0.004) and alcoholic cirrhosis (p < 0.001), and the proportion of caudate lobe significantly smaller in the patients with virus-related cirrhosis than in those with NASH (p < 0.001) and alcoholic liver cirrhosis (p < 0.001). In addition, the proportion of right lobe to the total liver was significantly larger in the patients with NASH than in those with alcoholic liver cirrhosis (p < 0.001). There was no significant difference in the proportion of posterior segment to the total liver in the patients with the three different etiologies (p > 0.05). Shaded boxes indicate the ranges of measured values between the 25th and 75th percentiles, horizontal lines inside boxes indicate medians, and the vertical bars (whiskers) indicate values of the 5th and 95th percentiles. The data were expressed as means ± standard deviations. * = p < 0.05 with multiple comparison tests. These descriptions apply to all of the box plots.

Fig. 6: The proportion of each segment to the total liver volume of three etiologies in Child-Pugh class A.
Comparison of CT images in Child-Pugh class A

Comparison of portal phase of axial CT images in patients of (a) control group, and with (b) virus-related, (c) alcoholic, and (d) NASH-related cirrhosis in Child-Pugh class A.

Virus-related (b), alcoholic (c), and NASH-related (d) cirrhosis shows atrophy of the medial (white asterisk) and anterior segments and right lobe (white dot), and hypertrophy of the lateral segment (black asterisk) and caudate lobe (black dot) as compared with the control group by multiple comparisons. In particular, the differences in the atrophy of the medial segment and hypertrophy of the caudate lobe among the etiologies are easily understandable in axial CT images.

Fig. 7: Comparison of portal phase of axial CT images in patients of control and cirrhosis in Child-Pugh class A.

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**Fig. 8:** The proportion of each segment to the total liver volume of the three etiologies in Child-Pugh class B. The proportion of lateral segment to the total liver was significantly smaller in the patients with NASH than in those with alcoholic cirrhosis ($p < 0.001$), the proportion of medial segment significantly larger in the patients with NASH than in those with alcoholic cirrhosis ($p = 0.045$), the proportion of anterior segment significantly larger in the patients with NASH than in those with alcoholic cirrhosis ($p = 0.003$), and the proportion of caudate lobe significantly smaller in the patients with virus-related cirrhosis than in those with alcoholic liver cirrhosis ($p = 0.001$). There were no significant differences in the proportion of posterior segment and right lobe to the total liver among the patients with the three different etiologies ($p > 0.05$).

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Fig. 9: Comparison of portal phase of axial CT images in patients with cirrhosis in Child-Pugh class B.

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The proportion of each segment to the total liver did not show significant differences among the patients with the three different etiologies.

**Fig. 10:** The proportion of each segment to the total liver volume of the three etiologies in Child-Pugh class C.

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Comparison of CT images in Child-Pugh class C

Comparison of portal phase of axial CT images in patients with (a) virus-related, (b) alcoholic, and (c) NASH-related cirrhosis in Child-Pugh class C.

Whole liver shows diffuse atrophy in all etiologies, and cirrhosis caused by all etiologies displayed atrophy of the medial segment (white asterisk), right lobe (white dot), and hypertrophy of lateral segment (black asterisk) and caudate lobe (black dot). These morphometric changes tended to be similar among the three etiologies, and no segments showed significant differences among them.

Fig. 11: Comparison of portal phase of axial CT images in patients with cirrhosis in Child-Pugh class C.

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Conclusion

Morphometric changes of cirrhosis display different patterns according to underlying etiology. Differences between etiologies decreased with progression of cirrhosis. Comprehension of the morphometric changes occurring in liver cirrhosis would be useful for predicting the etiology and determination of the stage of cirrhosis.
Personal information

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References


