Clinical significance of ultrasonographic imaging of the common hepatic arterial lymph node (No. 8 LN) in chronic liver diseases

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Abstract. In chronic liver diseases, the size of the portal lymph node and the common hepatic arterial lymph node (No. 8a LN) is often altered. The objective of this study was to investigate the relationship between the pathology of chronic liver diseases and the common hepatic arterial lymph nodes using an ultrasonographic diagnostic system. The subjects included 115 patients with hepatitis C (chronic hepatitis C, 75; liver cirrhosis C, 40), 31 patients with hepatitis B (chronic hepatitis B, 17; liver cirrhosis B, 14), 16 patients with primary biliary cirrhosis (PBC), 11 patients with autoimmune hepatitis (AIH), 29 patients with alcoholic hepatitis (Alc.LD) and 190 healthy adults with no abnormalities in liver function or inflammatory reactions (100 males and 90 females, age range 26-71 years, mean 49.2). The long and short axes of No. 8 LN were measured, and the value calculated by multiplying the two diameters was designated as the LN index (Fig. 1). The No. 8 LN appearance rate and LN index were significantly higher in the patients with hepatitis C, PBC and AIH than in the healthy subjects. When the LN index cut-off value was set to 50, alanine aminotransferase and aspartate aminotransferase were significantly higher in chronic hepatitis C (CHC) patients than in the healthy subjects. In addition, the LN and splenic indexes were significantly correlated in CHC patients, suggesting that the LX index is related to portal pressure increase with an elevation of sinusoidal pressure. The LN index after interferon therapy was significantly lower in complete responders than in non-responders. The No. 8 LN index may be closely related to the pathology of chronic liver diseases.

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Introduction

Ultrasonography is simple and non-invasive, and is essential for the examination of the liver in chronic liver diseases. The detection of intra-abdominal lymph nodes by ultrasonography is useful for the detection of lymph node metastasis from malignant tumors and the enlargement of lymph nodes due to diseases such as lymphoma. Additionally, a high appearance rate in patients with non-malignant tumors, particularly patients with chronic hepatitis B, C and primary biliary cirrhosis (PBC), has been reported since the advent of improvements in the performance of ultrasonographic test instruments (3-14). The common hepatic arterial lymph node (No. 8 LN) appearance rate on ultrasonography was reported to be 77-91% in patients with chronic hepatitis C (CHC) (3-12), 96% in patients with chronic hepatitis B (CHB) (14) and 74-100% in PBC patients (2,10). Additionally, No. 8 LN is detected by ultrasonography in 13-73% of healthy subjects (5,10,14). The usefulness of the measurement of No. 8 LN size for interferon treatment of hepatitis C has also been reported (6), as has a reduction in lymph node size with ursodeoxyxholic acid (UDCA) treatment of PBC (2). However, there are no reports on No. 8 LN imaging by ultrasonography in patients with chronic liver diseases and healthy subjects; the clinical significance of No. 8 LN imaging was investigated using the No. 8 LN index, which was calculated by multiplying the major and minor axes. This study was performed to clarify the correlation between the No. 8 LN appearance rate on ultrasonography and the size of No. 8 LN (No. 8 LN index), as well as between the No. 8 LN index and blood chemistry findings in patients with chronic liver diseases and healthy adults. Additionally, the relationship between interferon (IFN) therapy and the No. 8 LN index and the significance of the ultrasonographic No. 8 LN index were investigated.

Materials and methods

Subjects. The subjects were 192 patients with chronic liver diseases [hepatitis C, 115; hepatitis B, 21; PBC, 16; autoimmune hepatitis (AIH), 11; alcoholic hepatitis (Alc.LD), 29], who visited the Internal Medicine and Gastroenterology

Table I. Characteristics of patients with chronic liver disease and normal control subjects.

CLD	No. of subjects	Male		Female	
		No.	Age (mean)	No.	Age (mean)
Normal	190	100	26-71 (48.8)	90	29-62 (49.6)
Hepatitis type C	115	65	29-82 (61.3)	50	33-82 (63.9)
CHC	75	46	29-82 (58.5)	29	33-82 (61.9)
LCC	40	19	44-72 (60.0)	21	37-81 (66.5)
Hepatitis type B	21	13	28-71 (55.4)	8	41-70 (55.8)
CHB	17	10	28-77 (54.5)	7	41-64 (53.0)
LCB	4	3	35-71 (54.6)	1	70
PBC	16	1	64	15	47-74 (60.2)
AIH	11	2	68-79 (73.5)	9	43-73 (64.6)
Alc.LD	29	28	31-77 (63.1)	1	33

CLD, chronic liver disease; CHC, chronic hepatitis C; LCC, liver cirrhosis C; CHB, chronic hepatitis B; LCB, liver cirrhosis B; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; Alc.LD, alcoholic liver disease.

Departments of our hospital and underwent ultrasonography between March 2004 and September 2005. The patients were aged 26-82 years, with a mean age of 52.9. There were 109 males and 83 females. In addition, 241 healthy subjects (125 males, 49 years of age on average and 116 females, 50 years of age on average) that underwent health screening at our hospital and had no abnormalities in liver function or inflammatory reaction tests, nor any fatty liver or biliary disorders on ultrasonography, were investigated (Table I).

Methods. No. 8 LN was observed using the B-mode method. The sample point of the ultrasonography examination was placed at the center of the No. 8 LN on the common hepatic artery. During the imaging of No. 8 LN, No. 8a LN contacting the lower margin of the liver and the cranial side of the hepatic artery on the pancreatic head side was imaged in two directions, longitudinal and transverse scanning of the epigastric region. The maximum major and minor axes were measured and multiplied together, and the calculated value was designated as the LN index (Fig. 1). During its measurement, the spleen was imaged by left intercostal scanning. The maximum major and minor axes were measured and multiplied together, and the obtained value was designated as the splenic index. IFN was administered to 22 patients, and the outcomes were evaluated after treatment for 24 weeks. The LN index was simultaneously measured. The effect of IFN therapy was determined according to the following criteria: complete responders, negative qualitative hepatitis C (HCV)-RNA test and alanine aminotransferase (ALT) normalized at 24 weeks of IFN treatment; initial responders, positive qualitative HCV-RNA test, but ALT normalized at 24 weeks of IFN treatment; and non-responders, positive qualitative HCV-RNA test and ALT out of the normal range at 24 weeks of IFN treatment. The ultrasonography system used was SSA770A, Aplioo80 (Toshiba Medical Systems Corporation, Tokyo, Japan), and a convex-type probe (center frequency 3.5 and 5.0 MHz) was used. In blood testing, aspartate aminotransferase (AST), ALT, albumin (ALB), alkaline phosphatase (ALP), γ-glutamyl-transpeptidase (γ-GTP), cholinesterase (CHE) and platelets (PLT) were measured.

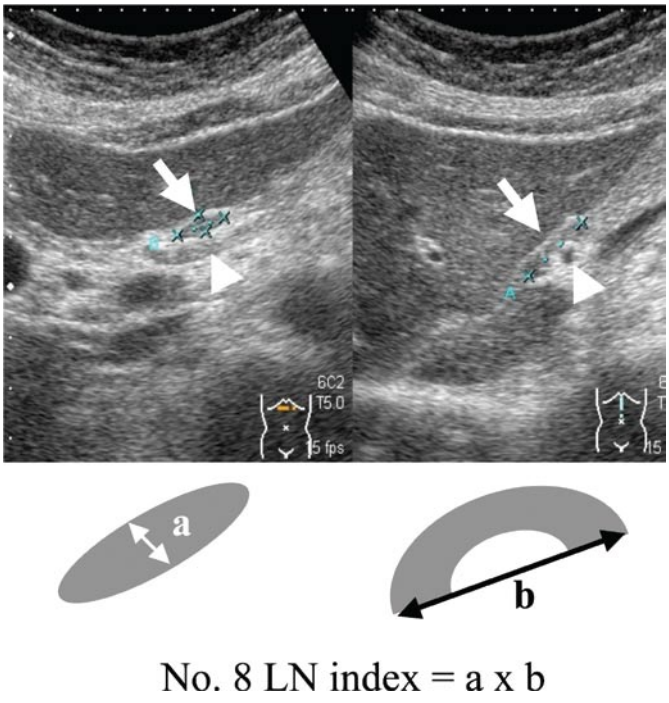

Figure 1. Measurement of the No. 8 LN index by ultrasonography. No. 8 LN, arrows; hepatic artery, arrowheads.

Statistical analysis. The χ_2 test was used for the evaluation of the lymph node appearance rate in relation to disease. One-way analysis of variance was used for the evaluation of the LN index, and Pearson's correlation coefficient test was used for correlation analysis. $P<0.05$ was regarded as significant.

Table II. The appearance rate of No. 8 LN in normal subject and chronic liver disease.

CLD	Rate (%) of No. 8 LN
Normal	18.4 (35/190)
HCV	84.2 (97/115)
HBV	38.1 (8/21)
PBC	93.8 (15/16)
AIH	81.8 (8/11)
Alc.LD	31.0 (9/29)

CLD, chronic liver disease; Normal, healthy subject; HCV, hepatitis C; HBV, hepatitis B; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; Alc.LD, alcoholic liver disease.

Table III. Association sensitivity and specificity index of No. 8 LN in chronic hepatitis C and normal control.

No. 8 LN index	Sensitivity	Specificity
<50	98	23
60	97	51
70	90	77
80	76	86
90	69	94
>100	53	97

Values are expressed as percentages (%).

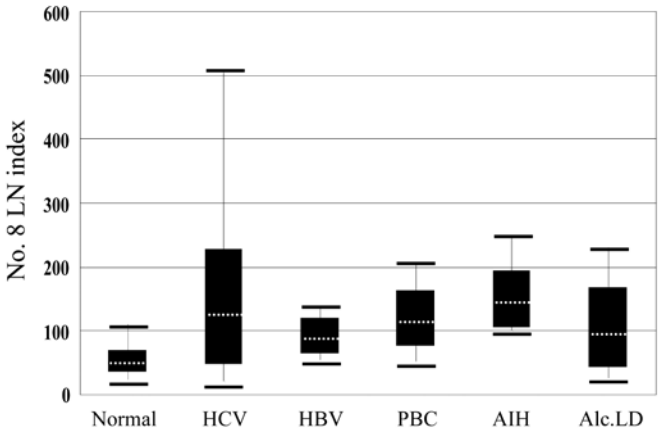

Figure 2. The appearance index of No. 8 LN in chronic liver disease. Normal, healthy subject; HCV, hepatitis C; HBV, hepatitis B; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; Alc.LD, alcoholic liver disease.

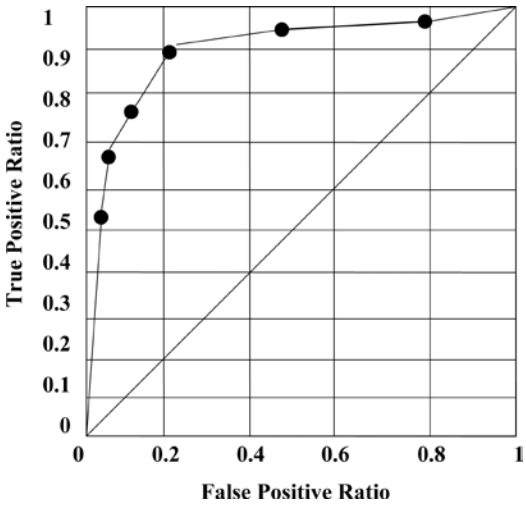

Figure 3. The appearance index of No. 8 LN in hepatitis C.

Results

No. 8 LN appearance rate and No. 8 LN index. In the healthy group, the No. 8 LN appearance rate and the size of No. 8 LN (No. 8 LN index) were 18.4% (35/190) and 51.4±16.7, respectively; no gender difference was noted.

Among patients with chronic hepatitis, the No. 8 LN appearance rate in the hepatitis C group was 84.2% (97/115), in the hepatitis B group 38.1% (8/21), in the PBC group 93.8% (15/16), in the AIH group 81.8% (8/11) and in the Alc.LD group 31.0% (9/29); the appearance rate was significantly higher in the hepatitis C, PBC and AIH groups compared to the healthy group (Table II).

The No. 8 LN index was 133±80.9 in the hepatitis C group, 101.6±38.8 in the hepatitis B group, 123.4±45.9 in the PBC group, 146.4±49.2 in the AIH group and 100.1±75.4 in the Alc.LD group; the LN index was significantly increased in all chronic liver disease groups compared to the healthy group (Fig. 2).

Establishment of a useful LN index for the differentiation of patients with hepatitis C and healthy individuals. The sensitivity and specificity, respectively, of the LN index calculated based on the findings from the hepatitis C and healthy groups were: 80 and 90% when the LN index was ≤50; 79.6 and 85.2% when the LN index was 60-70; and 77.7 and 82% when the LN index was ≥70 (Table III).

Correlation between the LN index and blood chemistry. No significant correlation was noted between the LN index and any of the seven blood chemistry test values in the hepatitis C group (Table IV). When the LN index cut-off value was set to 50 and the laboratory test values were compared between the CHC patients with an LN index of ≥50 and an LN index of <50, significant differences were noted in AST (51.1±39.4 vs. 32.9±14.2, P<0.014), ALT (53.4±41.2 vs. 35.9±23.1, P<0.031), ALP (301.8±84.4 vs. 231.2±52.6, P<0.001) and the splenic index (38.1±11.5 vs. 30.5±10.5, P<0.026) (Table V). In the patients with liver cirrhosis C (LCC), no significant correlation was noted between the LN index and any of the seven items. A significant positive correlation was noted between the LN and splenic indexes in HCV (r=0.27, P<0.05) (Fig. 4).

Evaluation of the LN index in interferon therapy. In 22 patients treated with IFN, the mean ± SD of the LN index was 32.7±15.8 in complete responders (n=11), 44.8±10.6 in

Table IV. Association between the No. 8 LN index (cut-off value 70) and clinical data (mean ± SD) in chronic hepatitis C.

Measurement	No. 8 LN (cut-off value 70)		
	>70 (n=52)	<70 (n=23)	P-value
AST	51.1±39.4	32.9±14.2	<0.014
ALT	53.4±41.2	35.9±23.1	<0.031
ALB	4.3±0.4	4.3±0.5	<0.991
ALP	301.8±84.4	231.2±52.6	<0.001
γ-GTP	60.0±56.5	59.5±47.2	<0.494
CHE	0.93±0.24	1.00±0.43	<0.289
PLT	176.7±90.2	181.1±56.4	<0.813
Splenic index	38.1±11.5	30.5±10.5	<0.026

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; ALP, alkaline phosphatase; γ-GTP,γ-glutamyl-transpeptidase; CHE, cholinesterase; PLT, platelets.

Table V. Association between the No. 8 LN index (cut-off value 70) and clinical data (mean ± SD) in liver chirrosis C.

Measurement	No. 8 LN (cut-off value 70)		
	>70 (n=27)	<70 (n=13)	P-value
AST	81.8±48.0	60.6±35.2	<0.172
ALT	58.2±39.6	46.0±32.4	<0.253
ALB	3.4±0.7	3.4±0.8	<0.481
ALP	433.6±246.7	392.5±137.1	<0.304
γ-GTP	56.5±41.5	91.3±124.8	<0.265
CHE	0.44±0.19	0.57±0.15	<0.273
PLT	69.8±31.0	107.7±93.1	<0.048
Splenic index	72.0±38.0	55.3±20.1	<0.194

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; ALP, alkaline phosphatase; γ-GTP,γ-glutamyl-transpeptidase; CHE, cholinesterase; PLT, platelets.

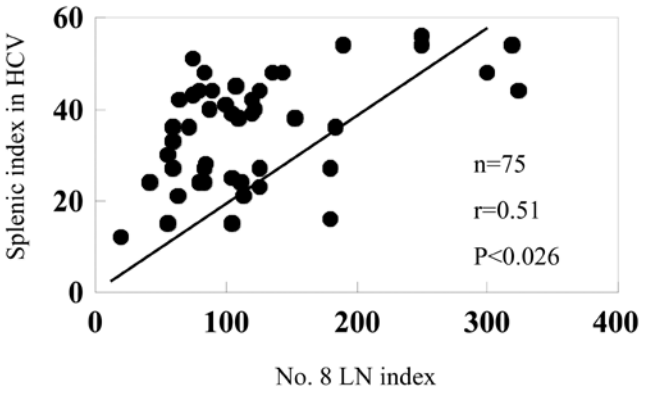

Figure 4. Correlation between the No. 8 LN index and splenic index in 115 hepatitis C (HCV) patients.

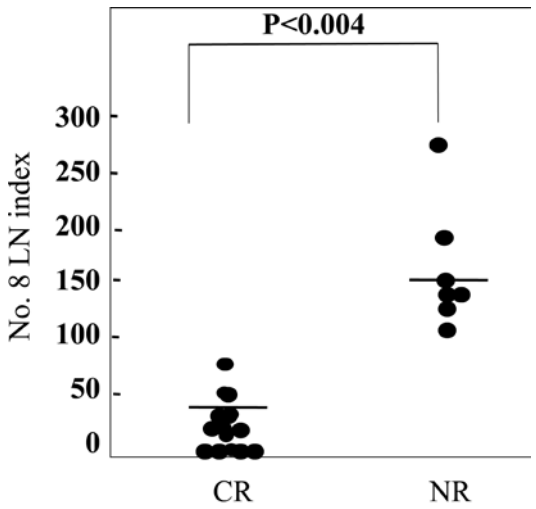

Figure 5. No. 8 LN index at end of treatment in 22 patients categorized according to IFN. CR, complete response; NR, non-response.

initial responders (n=4) and 150.4±52.3 in non-responders (n=7), with no significant difference between the complete and initial responders. The LN index was significantly lower in complete (P<0.004) and initial responders (P<0.005) than in non-responders (Fig. 5).

Discussion

No. 8 LN has previously been observed in 13-73% of healthy subjects (5,10,14). In the present study, the No. 8 LN appearance rate in healthy subjects was 18.4%. This is consistent with the previous reports, though tending towards the lower end of the range. This slightly decreased appearance rate in the healthy subjects may be due to differences between our No. 8 LN imaging method and those used in the other studies: in previous studies, the lymph nodes were scanned in the longitudinal direction only, while in the present study, the lymph node was scanned in longitudinal and transverse directions to accurately measure the minor axis, and only cases imaged in both scanning directions were determined to be No. 8 LN-positive.

No. 8 LN has previously been observed in 77-91% of CHC patients (3-12) and 96% of CHB patients (14). In our study, the No. 8 LN appearance rate was 84.2% in the hepatitis C group (n=115), similar to the findings of the previous reports, but only 36.8% in the hepatitis B group (n=21), which is lower than the findings in the previous reports. Regarding non-viral chronic hepatitis, a high No. 8 LN appearance rate (74-100%) in PBC has been reported (2,10). It was also high (94%) in the PBC group (n=16) in our study. No No. 8 LN appearance rate has been reported in AIH or Alc.LD. The appearance rate was high (80%) in the AIH group (n=11), but the rate (31%) in the Alc.LD group (n=29) was not significantly different from that in the healthy group.

Regarding lymph node size, there have been many reports of the relationship between chronic liver diseases and lymph nodes investigated by ultrasonography (8-12). However, none of the studies used the LN index (major x minor axis of the lymph node) for the side index lymph nodes, established the

cut-off value based on the sensitivity and specificity, or objectively evaluated lymph node size. We calculated the sensitivity and specificity in relation to size categories of the LN index from the findings in the CHC patients and healthy subjects, and compared these to objectively evaluate the lymph node size. At an LN index of 50, the sensitivity was 80% (60/75) and the specificity 92.5% (223/241), showing that the LN index was 50 or higher in 80% of the CHC patients, while it was lower than 50 in more than 90% of the healthy subjects. Thus, the cut-off value of the LN index was set to 50. This LN index cut-off value was also applicable for the other types of viral chronic hepatitis, and may be useful for the identification of viral chronic hepatitis by ultrasonography.

It has been reported that the lymph node size was correlated with an index of hepatocellular injury, AST, indices of cholestasis, ALP and γ-GTP, and a humoral immune reaction marker, IgM level, and was a secondary reaction of inflammation in hepatic lobules (2). Regarding CHC, Lyttkens *et al* (1) reported a positive correlation between the LN index and γ-GTP (r=0.53), and Spinetti *et al* (8) reported a significant correlation with ALT, though no significant correlation with liver function was noted in other reports (5,15). Thus, the correlation between lymph node size and laboratory data was inconsistent among the previous reports, and the lymph node may be observed even in healthy individuals. When the LN index cut-off value was set to 50, significant differences were noted with four laboratory test values: AST ($P<0.01$), ALT ($P<0.01$), ALP ($P<0.01$) and the splenic index ($P<0.01$), between the groups with an LN index of lower than 50 and 50 or higher. Based on these findings, the detection of a lymph node with an LN index of 50 or higher by ultrasonography suggests hepatitis C virus infection as well as abnormal liver function.

Wedemyer *et al* reported portal lymph node size and the effect of interferon treatment in CHC (6), in which non-responders accounted for 92% of cases with an increase in lymph node size after interferon treatment. Among cases with a decrease in the lymph node size, 57% were initial responders, while the lymph node size did not change in 44% of the initial responders. In our study, the LN index was significantly lower in complete and initial responders to IFN than in non-responders. Thus, the LN index may be utilized for monitoring IFN treatment. In CHC patients, the No. 8 LN index was lower than the cut-off value (50) in 87% (13/15) of the initial responders after IFN treatment, and in 100% (7/7) of the non-responders. Thus, the cut-off value established (No. 8 LN index 50) was valid, and may also be used for monitoring IFN treatment. Since hepatitis was sedated and ALT was normalized while HCV-RNA was positive in the initial responders, the lymph node size may decrease as ALT normalizes although HCV-RNA is positive. This does not contradict the absence of a correlation between lymph node size and the HCV-RNA level reported by Anton *et al* (13), as lymph node size may decrease due to the sedation of hepatocellular injury.

Ultrasonography is non-invasive and can easily be used to image No. 8 LN. The No. 8 LN index may be closely related to the degree of hepatocellular impairment in chronic liver diseases. When the LN index is 50 or higher, hepatitis virus tests such as the HCV test are necessary, and the LN index may be used as an index of the effect of therapy on chronic viral liver diseases.

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