

급성 A형간염에 의한 간내 강성도의 변화

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Abstract

Changes in liver stiffness during the course of acute hepatitis A

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Backgrounds/Aims: In some patients with chronic hepatitis, liver stiffness (LS) findings do not reflect fibrosis stage. This study was performed to evaluate whether acute liver inflammation could influence LS findings. **Methods:** Patients with acute hepatitis A admitted to our hospital were included. Hepatitis was classified on admission using serum ALT and bilirubin levels as inflammation phase, jaundice phase, or recovery phase. Patients who admitted during the recovery phase (whose ALT and bilirubin levels fell continuously during hospitalization) and therefore, their peak-ALT and peak bilirubin levels could not be determined were excluded. Enrolled patients underwent FibroScan during hospitalization and after discharge. **Results:** Seventy-six patients with acute hepatitis A were enrolled (median age, 29 years; 46 men and 30 women). Among them, 33 (43.4%) and 43 (56.6%) patients were admitted during the inflammation phase and jaundice phase, respectively. For patients admitted during the inflammation phase, mean (\pm SD) time from symptom-onset day to maximum ALT level was 7 (\pm 3) days. For all patients, mean time from symptom-onset to maximum bilirubin level was 11 (\pm 4) days. Mean LS during admission was 8.9 (\pm 3.3) kPa (median, 8.4 kPa). LS was significantly correlated with serum bilirubin level, which was the only factor found to be significantly associated with the increased LS ($>$ 7.08 kPa). In all patients, LS increased gradually from the symptom-onset and peaked at 8-9 days later. **Conclusions:** Severe hepatic inflammation can affect the LS findings and thus, care is required when assessing fibrosis stage using LS measurement in patients with severe inflammation. (*Korean J Hepatol* 2008;14:465-473)

Key words: Liver stiffness; Fibrosis; Inflammation; Acute hepatitis

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◇ Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; ULN: upper limit of normal; kPa, kilopascal; LS, liver stiffness.

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Introduction

The accurate assessment of the liver fibrosis extent is essential for predicting prognosis and determining appropriate management in patients with chronic liver diseases.¹ Liver biopsy is still considered the gold standard,² but it is invasive and can lead to life-threatening complications.^{3,4} Furthermore, its accuracy for assessing fibrosis is suspected due to sampling errors⁵⁻⁹ and intra- and interobserver discrepancies.⁹⁻¹¹

In contrast, liver stiffness (LS) determined using Fibroscan is entirely non-invasive, and reduces the potential for sampling errors,¹² because the liver volume measured is 100 times greater than that of liver biopsy specimens. In addition, LS measurements are reproducible with low intra- and interobserver variabilities.^{13,14} Furthermore, the correlation between LS and fibrosis stage seems to be unaffected by steatosis or degree of necroinflammation^{13,15,16} and several studies have suggested that LS is highly accurate for assessing liver fibrosis.^{12,15-22}

Unfortunately, in some patients with chronic hepatitis, LS and liver biopsy findings disagree and it has been suggested that this is usually caused by biopsy limitations and the design of the METAVIR grading system,^{13,23} rather than influence of liver inflammation on LS findings. However, the majority of patients enrolled in these studies had chronic hepatitis C with only marginal transaminases and bilirubin level deviations, and thus, the effects of such deviations on LS would have been difficult to determine.¹²⁻¹⁶ Furthermore, it was recently suggested that LS is dependent on liver inflammation in chronic hepatitis B¹⁴ and acute hepatitis.^{24,25}

Although the relation between liver inflamma-

tion and LS has been documented,^{24,25} relations between LS and transaminases and bilirubin levels remain unclear, because in previous studies cohort sizes were small and a focus was placed only on the relation between LS and alanine aminotransferase (ALT) levels. Therefore, we undertook this study to evaluate the changes in LS during the course of acute hepatitis A (AHA) and to identify those factors that influence LS.

Patients and Methods

1. Patients

This study is a retrospective observational study. We performed chart review of all consecutive patients with AHA hospitalized at our institution between September 2006 and March 2008. AHA was diagnosed when IgM antibody to hepatitis A virus was positive and serum ALT level was ≥ 10 times the upper limit of normal (ULN, 40 IU/L). Patients with previous or family history of liver disease were excluded, as were patients suspected of having another type of hepatitis based on the following findings: hepatitis B surface antigen, IgM antibody to hepatitis B core antigen, antibody to hepatitis C virus (HCV), HCV RNA quantification test, anti-nuclear antibody, anti-smooth muscle antibody, anti-LKM antibody, anti-mitochondrial antibody, copper, and ceruloplasmin. In addition, patients were excluded if peak bilirubin level could not be determined because it fell continuously during hospitalization.

At the time LS measurements were made, the following biochemical tests were also performed: serum aspartate aminotransferase (AST), ALT, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and bilirubin level.

2. Determination of acute hepatitis A phase

Serum ALT and bilirubin levels were checked every 1–3 days during hospitalization and the days when serum ALT and bilirubin peaked (peak-ALT and peak-bilirubin) were determined. In addition, the day of onset of acute hepatitis symptoms (Sx-onset) was determined by history taking.

Phases of AHA at time of hospitalization were determined as follows: inflammation phase – when a patient was hospitalized before peak-ALT, jaundice phase – when hospitalized after peak-ALT, but before peak-bilirubin.

3. Liver stiffness measurement

LS was measured using FibroScan (EchoSens, Paris, France) during hospitalization and after discharge. Measurements were performed on the right hepatic lobe through intercostal spaces with patients lying in dorsal decubitus with the right arm in maximal abduction. Results were expressed in kilopascals (kPa). LS values are median values of successful acquisitions. Only values based on at least 10 successful acquisitions with a success rate of at least 60% and with an interquartile range/LS lower than 20% were considered reliable.

A recent study found that LS in healthy subjects is 5.49 ± 1.59 kPa.²⁶ Therefore, the ULN of LS was set at 7.08 kPa (i.e. mean+one standard deviation), and thus higher LS values were considered elevated.

4. Statistical analysis

Statistical analysis was carried out using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). Quantitative variables are expressed as mean values \pm standard deviation (SD). Differences bet-

ween continuous variables were assessed using the Student's *t*-test or Mann-Whitney test. Spearman's correlation coefficients were used to analyze correlations between biochemical values and LS, and linear and binary regression analyses were used to identify factors independently associated with LS changes. To estimate the relation between LS and the course of AHA, LS scatter plots from Sx-onset (day of acute symptom onset) were analyzed by smoothing regression line with kernel estimation. Two-tailed *P* values of <0.05 were considered statistically significant.

Results

1. Baseline characteristics

Seventy-six patients (46 men and 30 women) with AHA were enrolled with their age (mean \pm SD) being 29 ± 5 years. Time from Sx-onset to hospitalization was 6 ± 3 days. Thirty-three patients (43.4%) were hospitalized during the inflammation phase and 43 (56.6%) during the jaundice phase. Time from Sx-onset to hospitalization was longer in patients hospitalized during the jaundice phase (7 ± 3 days) than in patients hospitalized during the inflammation phase (5 ± 3 days) ($P=0.002$).

Serum ALT peaked ($3,026 \pm 1,690$ IU/L) at 1 ± 1 days after hospitalization and at 7 ± 3 days after Sx-onset, and bilirubin level peaked (6.4 ± 2.8 mg/dL) at 5 ± 3 days after hospitalization and at 11 ± 4 days after Sx-onset. Although mean time from hospitalization to peak-ALT and peak-bilirubin were longer in patients hospitalized during the inflammation phase than in those hospitalized during the jaundice phase ($P<0.001$ and 0.007 , respectively), mean times from Sx-onset to peak-ALT or peak-bilirubin were not

Table 1. Clinical course of acute hepatitis A in the enrolled patients

	All patients (n=76)	Admission at inflammation phase (n=33)	Admission at jaundice phase (n=43)	P-value*
Duration from Sx-onset day to admission day (days)	6±3	5±3	7±3	<0.001
Peak-ALT level (IU/L)	3,026±1,690	3,104±1,792	2,967±1,626	0.912
Duration from admission day to peak-ALT day (days)	1±1	2±1	0±0	<0.001
Duration from Sx-onset day to peak-ALT day (days)	7±3	7±3	7±3	0.430
Peak-bilirubin level (mg/dL)	6.4±2.8	6.2±2.7	6.5±2.9	0.690
Duration from admission day to peak-bilirubin day (days)	5±3	6±3	4±3	0.003
Duration from Sx-onset day to peak-bilirubin day (days)	11±4	10±4	11±4	0.321

*Student's *t*-test was applied to the patients admitted during the inflammation and jaundice phases.

Data were expressed as means±S.D.

Sx-onset day, the day of acute hepatitis symptom onset; peak-ALT day, the day when serum ALT levels peaked; peak-bilirubin day, the day when serum bilirubin levels peaked.

significantly different for patients hospitalized during the inflammation and jaundice phase (Table 1).

2. Liver stiffness during hospitalization for AHA

LS measurement was performed at 2±3 days after hospitalization (at 8±4 days after Sx-onset). The LS values during hospitalization were 8.9±3.3 kPa and increased LS value (>7.08 kPa) was observed in 50 patients (65.8%). In terms of biochemical markers, only serum bilirubin was found to be significantly correlated with LS (Table 2, Fig. 1). Linear regression analysis with stepwise selection method was performed to select significant factors for LS, and serum bilirubin level was the only selected variable (β , 0.240; 95% confidence interval [CI], 0.018-0.526; *P*=0.036). Furthermore, when patients with normal LS were compared with those

Table 2. Relation between study variables and liver stiffness by Spearman's correlation analysis

	coefficient	P-value
AST	-0.051	0.660
ALT	0.153	0.188
Bilirubin	0.367	0.001
Duration from Sx-onset day to LSM-performed day	0.242	0.035
Duration from peak-ALT day to LSM-performed day	0.053	0.650
Duration from peak-bilirubin day to LSM-performed day	-0.117	0.313

AST, aspartate aminotransferase; ALT, alanine aminotransferase; Sx-onset day, the day of acute hepatitis symptom onset; peak-ALT day, the day when serum ALT levels peaked; peak-bilirubin day, the day when serum bilirubin levels peaked; LSM-performed day, the day when liver stiffness was measured.

with increased LS, only serum bilirubin level was found to be significantly different between

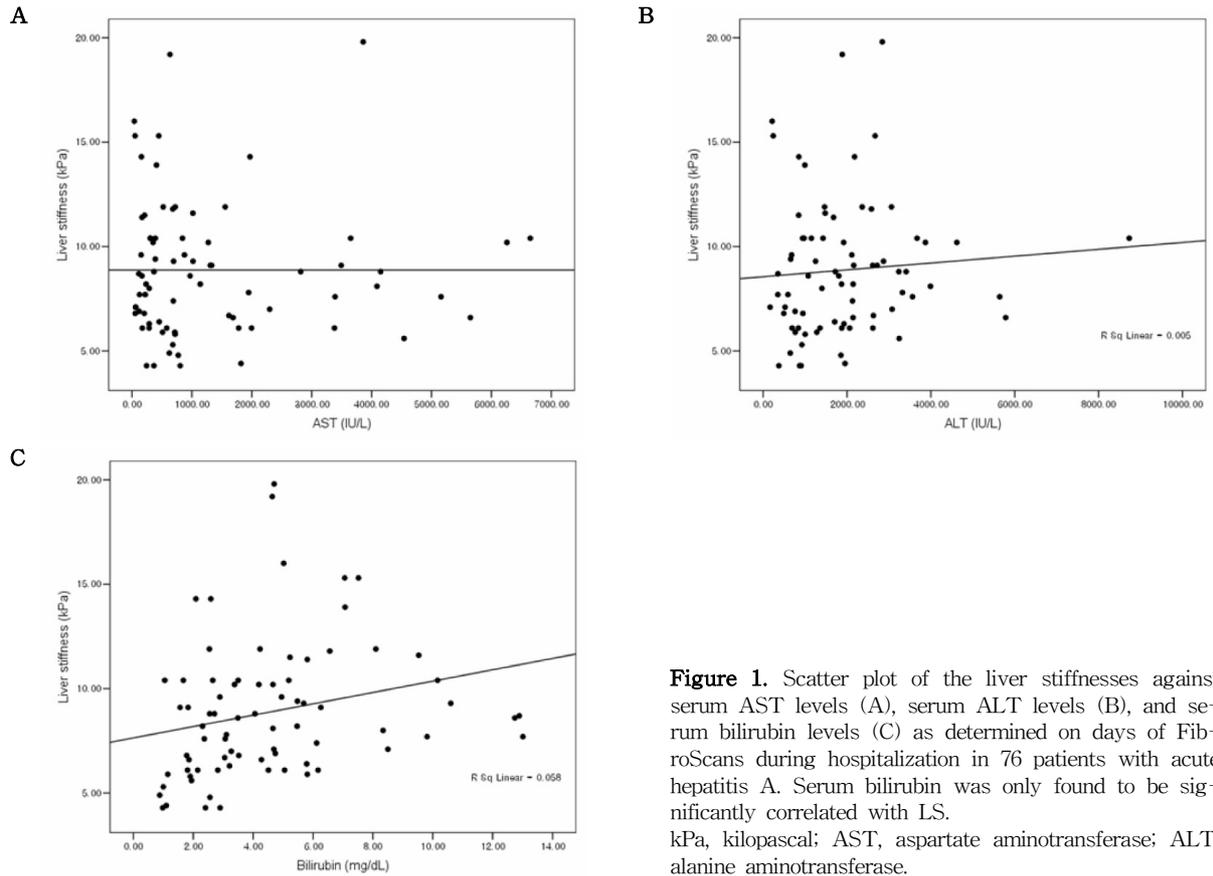


Figure 1. Scatter plot of the liver stiffnesses against serum AST levels (A), serum ALT levels (B), and serum bilirubin levels (C) as determined on days of FibroScans during hospitalization in 76 patients with acute hepatitis A. Serum bilirubin was only found to be significantly correlated with LS. kPa, kilopascal; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

two groups (Table 3). In addition, multivariate binary regression analysis also identified serum bilirubin level as being a significant factor of increased LS (odds ratio, 1.763; 95% CI, 1.198–2.594; $P=0.004$; Table 4).

3. Liver stiffness according to the duration from symptom-onset day to LSM-performed day

A second LS measurement was performed after discharge in 57 patients (75%) at 47 ± 16 days after Sx-onset and a third in 4 patients at 79 ± 12 days after Sx-onset. The LS values for these time points were 5.7 ± 1.7 kPa and 5.0 ± 0.5 kPa, respectively. When LS values were analyzed versus duration from Sx-onset, they were found to increase and peak 8–9 days later (Fig.

2). It then decreased 7.08 kPa at 20 days after Sx-onset and 5.5 kPa at 45 days after Sx-onset.

Discussion

This study was undertaken to explore the hypothesis that severe hepatic necroinflammation influences LS and to determine whether only ALT level is related to changes in LS, as has been previously claimed. Theoretically, it would be better if liver biopsies were used to stage liver fibrosis, but biopsies could not be performed in our patients because the presence of AHA is not included in the indications for liver biopsy. We tried to minimize the likelihood of including patients with advanced liver fibrosis by excluding those with a previous or family

Table 3. Biochemical findings between patients with normal LS and increased LS at admission

	Pts with normal LS (n=26)	Pts with increased LS (n=50)	P-value*
AST (IU/L)	1,244±1,404	1,354±1,674	0.776
ALT (IU/L)	1,642±1,170	2,099±1,563	0.178
Bilirubin (mg/dL)	2.9±1.6	5.4±3.1	<0.001
Duration from Sx onset day to LSM-performed day (days)	7±4	9±4	0.079
Duration from peak-ALT day to LSM-performed day (days)	2±2	2±2	0.716
Duration from peak-bilirubin day to LSM-performed day(days)	4±4	3±3	0.423

*Student's *t*-test was applied to the patients with normal LS and those with increased LS. Data were expressed as means±S.D. Normal LS was defined as 7.08 kPa. LS, liver stiffness; kPa, kilopascal; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Sx-onset day, the day of acute hepatitis symptom onset; LSM-performed day, the day when liver stiffness was measured; peak-ALT day, the day when serum ALT levels peaked; peak-bilirubin day, the day when serum bilirubin levels peaked.

Table 4. Relations between study variables and the increased liver stiffness (7.08 kPa) by multiple logistic regression analysis

Variables	β	SE	OR	95% CI	P-value
AST (IU/L)	0.00	0.00	1.00	1.00-1.00	0.811
ALT (IU/L)	0.00	0.00	1.00	1.00-1.00	0.070
Bilirubin (mg/dL)	0.57	0.20	1.76	1.20-2.60	0.004
Duration from Sx onset day to LSM-performed day (days)	-0.01	0.11	0.99	0.79-1.23	0.901
Duration from peak-ALT day to LSM-performed day (days)	0.36	0.23	1.44	0.92-2.25	0.112
Duration from peak-bilirubin day to LSM-performed day (days)	-0.04	0.11	0.96	0.78-1.18	0.707

kPa, kilopascal; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Sx-onset day, the day of acute hepatitis symptom onset; LSM-performed day, the day when liver stiffness was measured; peak-ALT day, the day when serum ALT levels peaked; peak-bilirubin day, the day when serum bilirubin levels peaked; SE, standard error; OR, odds ratio; CI, confidence interval.

history of liver disease and those suspected to have other types of hepatitis based on baseline examinations. Because AHA does not progress to chronic hepatitis and liver inflammation changes rapidly in AHA, we considered that patients with AHA offered the best model for evaluating the influence of liver inflammation on LS.

Actually, it has already been reported by several groups that LS is influenced by liver inflammation,^{14,24,25} but this might not be the only

relevant factor, because other factors might also make important contributions. Moreover, the identification of such factors would provide valuable information concerning the reliability of LS measurement in patients with chronic hepatitis.

Two recent studies on LS changes in patients with acute hepatitis (accepting limitations associated with small populations; 18 and 20 patients, respectively) are problematic in terms of study design.^{24,25} First, hepatitis B virus infections con-

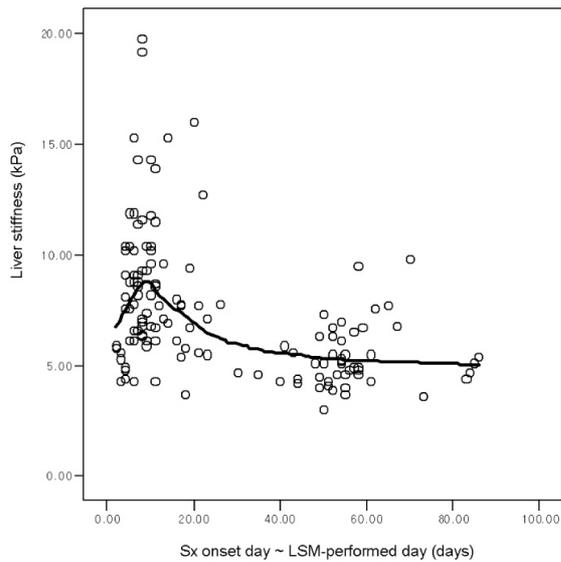


Figure 2. Liver stiffness versus time from symptom onset was presented by smoothed regression line with kernel estimation. LS values were found to gradually increase from Sx-onset, peak 8-9 days later, and then decrease.

stituted 44%²⁴ and 40%²⁵ of patients, respectively, and because liver biopsies were not performed in these patients, it was not determined whether acute exacerbation of chronic hepatitis B or acute hepatitis B caused the acute liver injuries. Patients with chronic hepatitis B may be asymptomatic when hepatic inflammation is not severe, and thus might be unaware that they are carriers of hepatitis B virus during periods of hepatic inflammation and progression of fibrosis. Furthermore, ALT and bilirubin levels are similar during acute hepatitis B and acute exacerbation of chronic hepatitis B. In addition, IgM antibody to HBV may be detected during acute exacerbation of chronic hepatitis B in some patients. Second, in one of these studies LS was measured 78 times in 20 patients with acute liver injury, and these results were then used to analyze the relationship between LS and serum ALT and bilirubin levels, which means that test results obtained at different times from indi-

vidual patients were treated in the same manner as results obtained from different patients.²⁵ Third, in the other study, only the relations between LS and serum AST or ALT were analyzed, and thus, no comment could be made concerning the effects of other factors like bilirubin level or acute hepatitis phase.²⁴

Our results showed that only serum bilirubin level was significantly correlated with LS during admission, which concurs with a previous report.²⁵ In this report, it was suggested that LS might be influenced by intrahepatic cholestasis. However, a recent study, which included patients with chronic cholestatic diseases (including primary biliary cirrhosis and primary sclerosing cholangitis), found that LS values were similar to those found in patients with chronic hepatitis C, although bilirubin levels were higher than in chronic hepatitis C.²⁰ These findings might suggest that LS is correlated with serum bilirubin level because serum bilirubin represents degree of hepatic necroinflammation more precisely than serum AST or ALT, and not because serum bilirubin represents the degree of intrahepatic cholestasis. Perhaps, increased cell densities caused by inflammatory cell infiltration and cell edema during acute hepatitis²⁷ could be responsible for increased LS during the acute phase. Our results suggest that LS increases for 8-9 days after Sx-onset, which lies between peak-ALT (6 days after Sx-onset) and peak-bilirubin (10 days after Sx-onset) and suggests that LS changes are dependent on the phase of acute hepatitis, and that they are not directly related to serum ALT or bilirubin levels.

In the present study, the upper limit of normal LS was defined as 7.08 kPa, because recently, Roulot et al²⁶ reported a mean LS in 429 healthy subjects of 5.49±1.59 kPa.²⁶ However, this upper

limit appears to be too high, because it is similar to previously reported cutoff value for significant fibrosis in chronic hepatitis.^{15,20,21} In their study,²⁶ 13.8% of all patients had metabolic syndrome, and no liver biopsy was performed, and thus, patients with liver fibrosis due to nonalcoholic steatohepatitis might have been included among their “healthy subjects”, which might have caused the upper limit of normal LS to have been overestimated. Accordingly, a further study is required to determine normal LS values in subjects without chronic hepatitis or nonalcoholic steatohepatitis.

In Summary, LS was found to transiently increase during the acute phase in hepatitis A for a period of 1-2 months. Our results also suggest fibrosis stages, as determined by LS measurement are likely to be overestimated in patients with chronic hepatitis in severe inflammatory phase, and LS measurement should be performed 1-2 months after an acute episode in patients with chronic hepatitis.

요 약

목적: 만성 간염 환자에서 liver stiffness (LS) 측정이 간섬유화를 평가하는 데 매우 유용한 검사로 알려져 있으나, 일부 환자에서는 LS와 실제 간섬유화 단계 사이에 상당한 차이가 관찰된다. 본 연구는 간의 괴사염증 정도가 이런 두 검사 결과 사이의 차이에 관여하는가를 평가하기 위해 시행하였다. **대상과 방법:** 급성 A형간염으로 본원에 입원한 환자를 대상으로 하였다. 입원 후 환자의 혈청 ALT 수치와 bilirubin 수치의 변화에 따라 환자의 입원 당시 급성 A형간염의 단계를 염증단계, 황달단계 및 회복단계로 분류하였으며, 회복단계에서 입원한 환자(입원 후 ALT 및 bilirubin 수치가 계속 감소하는 경우)는 본 연구에서 제외하였다. 입원 시 LS를 측정하였으며 상태가 호전되어 퇴원

한 후 추적하였다. LS값과 급성 A형간염의 진행단계, LS 측정 당시의 혈청 AST, ALT 및 bilirubin 수치와의 상관관계를 분석하였다. **결과:** 76명의 급성 A형간염 환자가 본 연구에 포함되었으며 연령의 중앙값은 29세였다(남자 46명 여자 30명). 이들 중 33명(43.4%)은 염증단계에, 43명(56.6%)은 황달단계에 입원하였다. 염증단계에 입원한 33명에서 급성 A형간염의 증상이 발생한 후 혈청 ALT가 최고치에 도달할 때까지의 기간은 7±3일이었으며, 전체 대상 환자에서 증상이 발생한 후 bilirubin이 최고치에 도달할 때까지의 기간은 11±4일이었다. 입원 중 측정된 LS값은 8.9±3.3 kPa였다. LS값은 bilirubin 수치와만 상관관계를 보였으며, LS 상승(>7.08 kPa)과 관련이 있는 인자도 bilirubin 수치 뿐이었다. 급성 간염의 증상이 발생한 후 LS값은 점차 상승하다가 증상 발생 후 8~9일 정도에 최고치에 도달한 후 점차 감소하였다. **결론:** 심한 간의 괴사염증은 LS를 높여 간섬유화 단계를 실제보다 과대평가할 수 있으므로 급성 악화를 동반한 만성 간염 환자에서 LS를 측정할 경우 결과의 판정에 유의하여야 할 것으로 생각된다.

색인단어: 간섬유화, 간 강성도, 괴사염증, 급성 간염

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