

BMJ Open Clinicobiochemical prediction of biopsy-proven cases of severe hepatic fibrosis in patients with chronic hepatitis C infection

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ABSTRACT

Objective: To evaluate clinicobiochemical factors predicting severe hepatic fibrosis in patients with chronic hepatitis C virus (HCV) infection.

Setting: Tertiary institution.

Participants: 859 treatment-naïve Korean patients with HCV who underwent liver biopsy. Severe fibrosis was defined as fibrosis stage ≥ 3 based on the METAVIR system.

Primary outcome measures: Clinicobiochemical factors predicting severe hepatic fibrosis.

Results: The median serum alanine aminotransferase (ALT) level was 68 IU/L and body mass index (BMI) was 24.2 kg/m². Severe fibrosis was observed in 326 (39.7%) of the 859 patients. The frequencies of severe fibrosis were 0%, 37.8%, 41.9% and 42% in patients with serum ALT concentrations (IU/L) of ≤ 20 , 20–30, 30–40 and >40 ($p < 0.01$), respectively, and 10.7%, 19.8%, 30.5%, 39.2% and 55.6% in patients < 30 , 30–40, 40–50, 50–60 and ≥ 60 years old, respectively ($p < 0.01$). Categorised age in years (50–60 (OR 4.26, $p = 0.03$) and ≥ 60 (OR 7.53, $p < 0.01$) compared with < 30), categorised ALT level in IU/L (20–30 (OR 16.76, $p < 0.01$), 30–40 (OR 20.02, $p < 0.01$) and > 40 (OR 21.49, $p < 0.01$) compared with ≤ 20) and BMI > 27.5 kg/m² (OR 1.65, $p = 0.03$) were independently related to severe fibrosis in patients with chronic HCV. The severe fibrosis rate was 60.6% in patients aged ≥ 50 years with ALT > 20 IU/L and BMI > 27.5 kg/m².

Conclusions: More advanced age (≥ 50 years), obesity and serum ALT > 20 IU/L are associated with severe fibrosis in patients with chronic HCV. Anti-HCV therapy may be considered for these patients without histological confirmation, regardless of HCV genotype. A wait-and-see policy may be justified for patients with serum ALT ≤ 20 IU/L.

INTRODUCTION

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease.^{1 2} An estimated 70–85% of patients with HCV infection develop chronic hepatitis³ and approximately 30% of these patients progress to liver cirrhosis over two or three decades following the

Strengths and limitations of this study

- Severe hepatic fibrosis was present in almost 40% of the patients with chronic hepatitis C virus with serum alanine aminotransferase (ALT) level greater than 20 IU/L.
- However, severe hepatic fibrosis was not observed in any patient with a serum ALT level of 20 IU/L or less.
- Furthermore, older age (≥ 50 years), obesity and elevated levels of serum ALT (> 20 IU/L) were closely associated with severe hepatic fibrosis in these patients.
- In particular, severe hepatic fibrosis was observed in about 60% of patients aged ≥ 50 years with serum ALT concentrations > 20 IU/L and body mass index (BMI) > 27.5 kg/m².
- Thus, our findings suggest that the presence of these high-risk factors for severe hepatic fibrosis may justify an active antiviral approach without liver biopsy findings.
- Major limitation of the current study is that the data are from a single institution and a single ethnic type.
- Because of the differences in procedures for serum ALT measurement in different clinical laboratories and the fact that Asian BMI cut-off points differ from those of Western populations, further multicentre and multiethnic studies are required for external validation and wider use of our estimates.

infection.⁴ It is known that the stage of fibrosis observed in the initial liver biopsy can predict the likelihood of progression to cirrhosis in patients with chronic HCV.⁵ Furthermore, American Association for the Study of Liver Disease (AASLD) guidelines advise antiviral treatment for patients with severe fibrosis confirmed by liver biopsy, if serum HCV RNA results are positive.⁶ Thus, it is important to differentiate severe hepatic fibrosis from non-severe fibrosis in order to determine whether antiviral treatment should be initiated.

To assess the extent of hepatic fibrosis in patients with chronic HCV infection, liver biopsy has been the standard test, despite the possible complications.^{7,8} However, the issue of whether patients with chronic HCV should undergo routine liver biopsy to determine the extent of fibrosis remains controversial.⁹ Furthermore, liver biopsy may be unnecessary for patients with genotype 2 or 3 chronic HCV because these individuals achieve a high sustained virological response (SVR) rate of more than 80% to standard therapy.^{6,10–12} However, there is an ongoing debate about whether routine liver biopsy is warranted for patients with genotype 1 chronic HCV, whose antiviral response rate is still about 66–75% after triple therapy with pegylated interferon, ribavirin and protease inhibitor, which is a standard of care recently set by global guidelines.^{13–17}

A previous study in a European population suggested that about 65% of patients with chronic HCV with normal alanine aminotransferase (ALT) levels have a degree of hepatic fibrosis of at least F1 based on the METAVIR scoring system.¹⁸ However, it is not clear whether the extent of hepatic fibrosis, especially severe fibrosis, in Asian patients with chronic HCV can be based on data from Western populations. Furthermore, to date, there are only limited data on definite clinical or biochemical factors that can predict the development of severe hepatic fibrosis in Asian patients with chronic HCV infection, although the efficacy of proposed non-invasive fibrosis indexes has been validated in such patients.¹⁹

The aim of the current study, therefore, was to assess the extent of severe hepatic fibrosis in Korean patients with chronic HCV. We also aimed to identify prehistological clinical and biochemical factors predictive of severe hepatic fibrosis.

PATIENTS AND METHODS

Study subjects

Between January 1995 and December 2010, 937 consecutive patients were diagnosed as having chronic HCV infection at Asan Medical Center and underwent liver biopsy for evaluation of liver histology before antiviral treatment was initiated. All the patients were positive for anti-HCV antibody and HCV RNA, but none had any history of antiviral treatment for HCV. The diagnosis of chronic HCV infection was based on the AASLD criteria.⁶

Of a total of 937 patients, 78 were excluded because they were under 16 years old (n=10), were co-infected with hepatitis B virus (n=9), had a history of renal (n=3) or liver transplantation (n=43), or malignancy (lymphoma (n=1), cholangiocarcinoma (n=4), lung cancer (n=1) and melanoma (n=1)), or consumed more than 40 g of alcohol per week (n=6). Finally, 859 patients were enrolled in the present study, which was approved by the Institutional Review Board of Asan Medical Center (protocol number: 2012-0404).

Table 1 Baseline characteristics of patients with chronic HCV infection

Variables	HCV (n=859)
Age (years), n (%) [*]	52 (19–77)
<30	28 (3.3)
≥30 and <40	111 (12.9)
≥40 and <50	223 (26.0)
≥50 and <60	263 (30.6)
>60	234 (27.2)
Gender (male), n (%)	487 (56.7)
BMI (kg/m ²), n (%) [*]	24.2 (13.9–38.5)
<23	303 (35.3)
≥23 and <27.5	424 (49.4)
≥27.5	132 (15.4)
Genotype, n (%)	
1	396 (46.1)
2 or 3	441 (51.3)
Others	22 (2.6)
AST (IU/L), n (%) [*]	59 (10–939)
≤20	43 (5.5)
>20 and ≤30	112 (21.5)
>30 and ≤40	112 (13.0)
>40	592 (68.9)
ALT (IU/L), n (%) [*]	68 (9–961)
≤20	73 (8.5)
>20 and ≤30	90 (10.5)
>30 and ≤40	86 (10.0)
>40	610 (71.0)
Platelet count (×10 ³ /mm ³) [*]	165 (56–385)
APRI [*]	0.92 (0.1–43.2)
FIB-4 [*]	2.1 (0.2–53.1)
Cholesterol (mg/dL) [*]	154 (38–274)
DM, n (%)	12 (1.4)

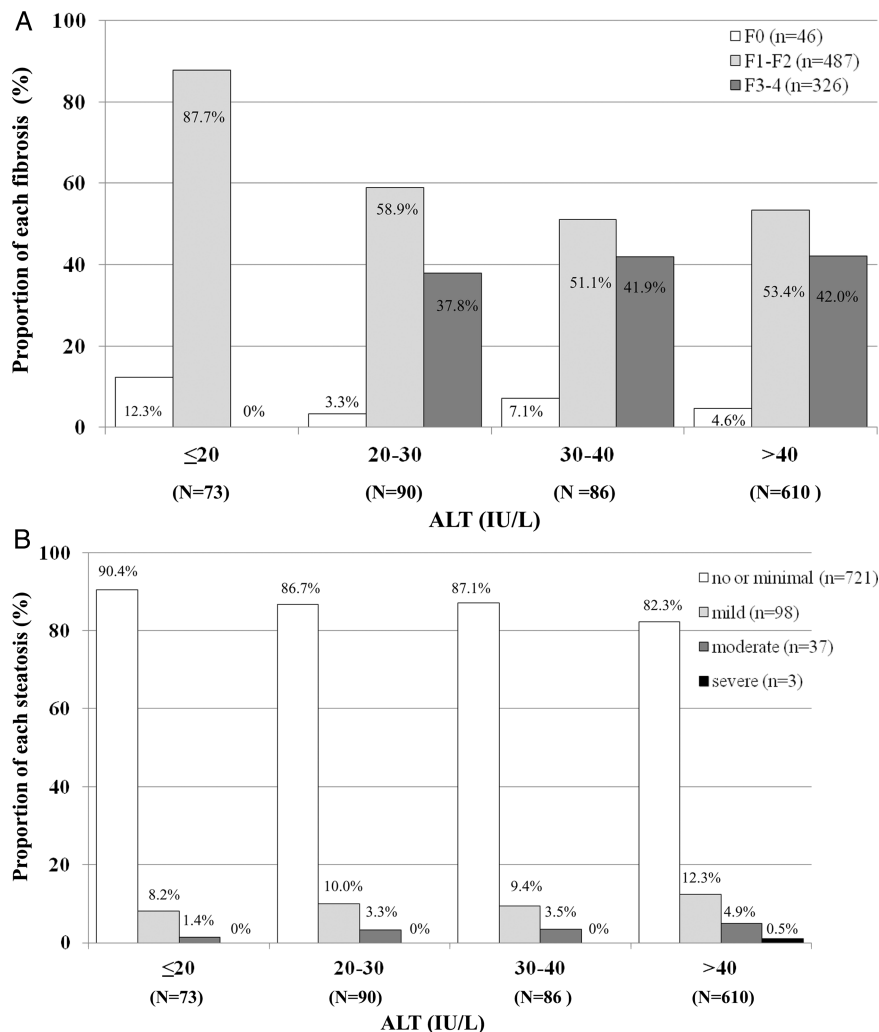
^{*}Median (range).

ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; DM, diabetes mellitus; FIB-4, fibrosis-4; HCV, hepatitis C virus.

Laboratory data

The activities of serum biomarkers such as aspartate aminotransferase (AST), ALT and glucose were measured at the time of initial liver biopsy before antiviral treatment was initiated. Data were also obtained before liver biopsy on age, gender, body weight (kg), height (m), body mass index (BMI), hepatitis B surface antigen and antibody, serological test results for HIV, anti-HCV antibody and HCV RNA (RT-PCR with a single stranded linear probe; Abbott RealTime kit, Abbott) and HCV genotype (RFMP, GeneMatrix, Yongin, Korea). All measurements of serum activities of AST and ALT were performed by the same method and analysed using a TBA 200FR NEO autoanalyser (Toshiba, Tokyo, Japan). In our institution, the conventional threshold of normal serum ALT has been identified as 40 IU/L for males and females, as previously described.²⁰ BMI (kg/m²) was calculated from the formula weight/(height)², and the patients were categorised as normal (18.5–23 kg/m²), overweight (23–27.5 kg/m²) or obese (≥27.5 kg/m²), based on BMI values for Asian populations.²¹ APRI (AST-to-platelet

Figure 1 Histological findings in patients with chronic hepatitis C virus infection. The proportion of individuals with severe fibrosis (A) and steatosis (B) are shown according to serum alanine aminotransferase (ALT) level.



ratio index) and FIB-4 (fibrosis-4) were also calculated as non-invasive fibrosis markers.^{22 23}

Preparation and evaluation of liver biopsy specimens

The clinician's decision for liver biopsy before treatment was usually based on HCV genotype and need for the information on antiviral prognosis. Before the procedure, written informed consent was obtained from all patients. After liver biopsy, patients were carefully monitored every 1 h for the first 4 h, and thereafter every 6 h during 1 day. Two or more biopsy specimens, each approximately 1.5 cm in length, were obtained from every patient. All liver biopsy specimens were fixed in 10% neutral-buffered formalin. Sections were cut at 3–4 μ m thickness and stained with H&E, Prussian blue and Masson's trichrome stain. All pathological findings were retrospectively obtained by careful review of pathologists' clinical records under the supervision of one senior expert pathologist (EY) who confirmed the final pathological diagnosis. Fibrosis stage and activity grade of the liver specimens were determined based on previously published guidelines.^{24 25} Severe fibrosis was defined as fibrosis stage ≥ 3 based on the METAVIR

scoring system,^{24 25} which is also described in the AASLD guidelines.⁶ Fatty changes were categorised as none or minimal (<5%), mild ($\geq 5\%$ and <30%), moderate ($\geq 30\%$ and <60%) or severe ($\geq 60\%$).²⁶

Statistical analyses

The basic clinical characteristics of the patients are expressed as median (range) and frequency. Differences between categorical or continuous variables were analysed using the χ^2 test, Fisher's exact test, or Student t test. Multivariate analysis by stepwise linear and logistic regression analysis was performed to assess the predictors of severe hepatic fibrosis in patients. A p value of less than 0.05 (two-tailed) was considered statistically significant in all analyses, which were performed with SPSS V.18.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Baseline clinical and virological characteristics

Baseline characteristics of the 859 patients are shown in table 1. The median age of the patient was 52 years (range 19–77 years) and 487 (56.7%) patients were male. The most common HCV genotypes were

genotypes 2 and 3, observed in 441 (51.3%) patients, followed by genotype 1, in 396 (46.1%) patients. Median BMI was 24.2 kg/m², and 349 patients (40.6%) were overweight or obese. The median serum ALT level was 68 IU/L, and 249 (29%) patients had normal serum ALT concentrations (≤ 40 IU/L). Only 1.4% of the patients had underlying diabetes mellitus (DM). Median scores of APRI and FIB-4 were 0.92 and 2.1, respectively. Severe hepatic fibrosis was not observed in any patient with serum ALT concentration ≤ 20 IU/L (table 1).

Distribution of severe fibrosis and steatosis according to categorised serum ALT levels

The frequencies of severe fibrosis were 0%, 37.8%, 41.9% and 42% in patients with serum ALT levels of ≤ 20 , 20–30, 30–40 and >40 IU/L ($p < 0.01$), respectively (figure 1A), and the frequencies of mild to severe steatosis were 9.6%, 13.3%, 12.9% and 17.7% in the same patient groups, respectively ($p = 0.07$; figure 1B).

Clinicobiochemical factors associated with severe hepatic fibrosis

Severe hepatic fibrosis was observed in 326 (39.7%) patients. A higher proportion of these patients were older ($p = 0.001$) and had higher BMI ($p = 0.035$), AST ($p = 0.001$) and ALT ($p < 0.001$), APRI (< 0.001) and FIB-4 (< 0.001) levels than the individuals without severe hepatic fibrosis. Gender proportion ($p = 0.093$), HCV genotype ($p = 0.203$) and presence of DM ($p = 0.068$) were not significantly different in patients with or without severe hepatic fibrosis (table 2).

Multivariate analysis of factors predicting development of severe hepatic fibrosis

In the multivariate analysis, categorised age in years (50–60 (OR 4.26, $p = 0.03$) and ≥ 60 (OR 7.53, $p < 0.01$) compared with < 30), categorised ALT levels in IU/L (20–30 (OR 16.76, $p < 0.01$), 30–40 (OR 20.02, $p < 0.01$) and > 40 (OR 21.49, $p < 0.01$) compared with ≤ 20) and BMI > 27.5 kg/m² (OR 1.65, $p = 0.03$) were independently related to the occurrence of severe hepatic fibrosis in these patients with chronic HCV (table 3). Other individual components of APRI or FIB-4 such as AST level and platelet count were not significantly maintained in multivariate analysis. The number of patients with age ≥ 50 years, ALT > 20 IU/L and BMI > 27.5 kg/m² was 71 (8.3%) of all 857 included patients. Of these 71 patients, 43 (60.6%) had severe hepatic fibrosis, accounting for 13% among all of the cases with severe fibrosis.

DISCUSSION

We have shown that while severe hepatic fibrosis was present in almost 40% of the patients with chronic HCV with serum ALT levels greater than 20 IU/L, it was absent in all patients with serum ALT levels of 20 IU/L or below. This finding did not depend on any prebiopsy clinicometabolic parameters identified as associated with

Table 2 Comparison of clinical parameters according to presence of severe fibrosis in patients with HCV

Variables	Severe fibrosis		p Value*
	Absent (n=533) Group A†	Present (n=326) Group B‡	
Age (years), n (%)			0.001
<30	25 (4.7)	3 (0.9)	
≥ 30 and <40	89 (16.7)	22 (6.7)	
≥ 40 and <50	155 (29.1)	68 (20.9)	
≥ 50 and <60	160 (30.0)	103 (31.6)	
≥ 60	104 (19.5)	130 (39.9)	
Male gender, n (%)	312 (58.5)	175 (53.7)	0.093
BMI (kg/m ²), n (%)			0.035
<23	198 (37.3)	105 (32.0)	
≥ 23 and <27.5	264 (49.7)	160 (48.8)	
≥ 27.5	69 (13.0)	63 (19.2)	
HCV genotype			0.203
1	233 (43.7)	163 (50.0)	
2 or 3	286 (53.7)	155 (47.5)	
others	14 (2.6)	8 (2.5)	
AST (IU/L), n (%)			0.001
≤ 20	41 (7.7)	2 (0.6)	
> 20 and ≤ 30	93 (17.4)	19 (5.8)	
> 30 and ≤ 40	86 (16.1)	26 (8.0)	
> 40	313 (58.7)	279 (85.6)	
ALT (IU/L), n (%)			<0.001
≤ 20	73 (13.7)	0 (0)	
> 20 and ≤ 30	56 (10.5)	34 (10.4)	
> 30 and ≤ 40	50 (9.4)	36 (11.0)	
> 40	354 (66.4)	256 (78.5)	
Platelet count ($\times 10^3/\text{mm}^3$)§	133.3 \pm 52.7	190.3 \pm 55.2	<0.001
APRI§	1.03 \pm 1.34	2.24 \pm 3.41	<0.001
FIB-4§	2.13 \pm 1.79	5.49 \pm 6.56	<0.001
DM, n (%)	4 (0.8)	8 (2.5)	0.068
Cholesterol (mg/dL)§	155.7 \pm 33.1	157.1 \pm 30.8	0.525

*pvalue for difference between groups A and B.

†Patients with fibrosis stage 0–2.

‡Patients with fibrosis stage 3–4.

§Mean (\pm SD).

ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; DM, diabetes mellitus; FIB-4, fibrosis-4; HCV, hepatitis C virus.

serum ALT activity in previous studies.^{27 28} It was also notable that older age (≥ 50 years) and obesity, as well as higher than normal levels of serum ALT (> 20 IU/L), were closely associated with severe hepatic fibrosis in these patients. In particular, severe hepatic fibrosis was observed in about 60% of patients aged ≥ 50 years with serum ALT concentrations > 20 IU/L and BMI > 27.5 kg/m², and these patients accounted for 13% among all of the cases with severe fibrosis.

Consensus has already been reached about the necessity for initiating anti-HCV treatment in patients with chronic HCV with moderate hepatitis or severe fibrosis, especially in young patients with a long expected life

Table 3 Multivariate analysis of factors predicting severe fibrosis in patients with HCV

Variables	Univariate analysis			Multivariate analysis*		
	OR	95% CI	p Value	OR	95% CI	p Value
Age (years)						
<30 (control)	–	–	–	–	–	–
≥30 and <40	2.06	0.57 to 7.45	0.27	1.86	0.49 to 7.07	0.36
≥40 and <50	3.66	1.07 to 12.52	0.04	2.87	0.79 to 10.37	0.11
≥50 and <60	5.37	1.58 to 18.22	0.01	4.26	1.19 to 15.32	0.03
≥60	10.42	3.06 to 34.46	<0.01	7.53	2.09 to 27.11	<0.01
Male gender	1.22	0.92 to 1.61	0.16	–	–	–
AST (IU/L)						
≤20 (control)	–	–	–	–	–	–
>20 and ≤30	4.19	0.93 to 18.82	0.06	0.95	0.22 to 4.41	0.95
>30 and ≤40	6.19	1.40 to 27.38	0.02	0.97	0.22 to 4.22	0.97
>40	18.27	4.38 to 76.24	<0.01	3.36	0.78 to 14.34	0.10
ALT (IU/L)						
≤20 (control)	–	–	–	–	–	–
>20 and ≤30	19.55	4.96 to 93.59	<0.01	16.76	3.39 to 82.66	<0.01
>30 and ≤40	20.56	5.88 to 111.07	<0.01	20.02	4.01 to 84.73	<0.01
>40	25.67	6.24 to 105.62	<0.01	21.49	4.34 to 85.43	<0.01
BMI (kg/m ²)						
<23 (control)	–	–	–	–	–	–
≥23 and <27.5	1.14	0.84 to 1.55	0.39	0.99	0.71 to 1.39	0.97
≥27.5	1.72	1.14 to 2.61	0.01	1.65	1.05 to 2.61	0.03
DM	2.67	0.39 to 18.17	0.32	–	–	–
Cholesterol (mg/dL)	0.99	0.99 to 1.01	0.38	–	–	–

*Logistic regression model; patients, n=859; event, severe hepatic fibrosis (n=326).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DM, diabetes mellitus.

span ahead.⁶ However, the necessity for routine liver biopsy to evaluate fibrosis stage before anti-HCV treatment remains controversial. Aside from the fact that anti-HCV treatment has potential adverse effects, it is not effective for all patients, and is relatively expensive,²⁹ the biopsy procedure itself is associated with adverse effects such as pain, bleeding and bowel perforation,⁸ which may incur additional medical care costs and cause patients distress and anxiety.³⁰ In our series, about one-fourth of the biopsied patients experienced mild or moderate abdominal pain after liver biopsy, although there were no serious complications requiring a long hospital stay. Indeed, some patients may hesitate to receive anti-HCV treatment based on histological evidence, even despite only the minor chance of serious adverse events occurring owing to biopsy. Thus, simple clinicobiochemical factors capable of predicting severe hepatic fibrosis without pathological evidence could be practically helpful in deciding on the treatment for patients with chronic HCV.

Although previous studies have evaluated factors associated with histological findings of patients with chronic HCV in Western populations,^{18 31–34} there is still a lack of data about whether the findings can be confidently extrapolated to Asian patients. Interestingly, our Asian data show that severe hepatic fibrosis was not present in patients with low normal serum ALT levels (≤20 IU/L), supporting a wait-and-see approach for these patients,

particularly those with clinical or genetic parameters related to suboptimal antiviral treatment response.⁶ In contrast, more advanced age (≥50 years), obesity and serum ALT levels >20 IU/L were independent predictors of significant hepatic fibrosis. These findings suggest that immediate anti-HCV treatment without performing a liver biopsy may be beneficial for patients above 50 years (albeit not for elderly patients (>65 years), weighing the potential risks and benefits³⁵), especially for obese genotype 2 or 3 patients with serum ALT concentrations >20 IU/L, because more than 80% of patients with HCV with genotype 2 or 3 achieve an SVR to standard-of-care treatment.¹² Given the better antiviral response of Asian patients, who have the favourable *IL28B* genotype more frequently than Western individuals,³⁶ it may be preferable to initiate antiviral treatment for young Asian patients infected with genotype 1 HCV without pathology results if serum ALT levels are above 20 IU/L. Moreover, our results suggest that even in patients with genotype 1 HCV infection, which is a well-known predictor of negative antiviral treatment response,⁶ high-risk factors for significant hepatic fibrosis such as serum ALT levels of >20 IU/L, age ≥50 years and obesity may be deemed to justify an active antiviral approach, preferably with triple regimens, without liver biopsy findings.

We observed severe hepatic fibrosis in about 40% of the patients with normal ALT levels (ie, less than 40 IU/L).

This rate was similar to that in patients with elevated ALT levels. This suggests that the decision to initiate anti-HCV treatment should not be based simply on serum ALT levels, especially in patients with serum ALT concentrations >20 IU/L. Likewise, patients with serum ALT of 20–40 IU/L should not be excluded from antiviral therapy simply because of normal ALT levels. Moreover, liver biopsy may be required for decision-making regarding antiviral treatment when serum ALT levels are 20–40 IU/L in older (>50 years) and obese patients who are reluctant to receive treatment.

It has been reported that host factors such as age and obesity are associated with the development of hepatic fibrosis,^{5 37} and in this respect the outcomes of our study are similar to those of previous studies.^{5 37} Although non-invasive tests such as elastography, non-alcoholic fatty liver disease fibrosis score, and APRI or the FIB-4 score have been developed to estimate hepatic fibrosis, their accuracy has not been sufficiently validated.^{22 23 38 39} Moreover, these tests involve high cost and additional calculations. However, we have identified inexpensive and simple clinical parameters that are not expensive to measure and that can aid decision-making about severe hepatic fibrosis.

Despite the extensive analyses using large scale pathology-based data sets, a major limitation of the current study is that the data are from a single institution and a single ethnic type. Because of the differences in procedures for serum ALT measurement in different clinical laboratories and the fact that Asian BMI cut-off points differ from those of Western populations,^{21 40} further multicentre and multiethnic studies are required for external validation and wider use of our estimates. In addition, our cohort did not include patients with HCV-infection who received antiviral treatment without resorting to biopsy or who were never treated, which may introduce a selection bias. Finally, observational variations among pathologists in histological evaluation should be taken into account when interpreting the present results and further applying them in clinical practice.

In conclusion, advanced age (≥ 50 years), obesity and serum ALT levels >20 IU/L are closely associated with the development of severe hepatic fibrosis in Korean patients with chronic HCV infection. These findings could facilitate clinical decision-making in the management of patients with HCV-infection.

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