Table 1 Comparison of clinical factors between 642 anti-hepatitis C virus (HCV)-positive participants with and without clearance of serum HCV RNA

Clinical factors	Clearance of HCV RNA		p Value
	Yes	No	
Case numbers, n (%)	164 (25.5)	478 (74.5)	
Sex			0.449
Male, n (%)	56 (23.8)	179 (76.2)	
Female, n (%)	108 (26.5)	299 (73.5)	
Mean (SD) age (years)	56.4 (5.9)	56.4 (5.9)	0.987
Mean (SD) BMI (kg/m ²)	24.7 (3.3)	24.7 (3.8)	0.961
>27, n (%)	32 (22.5)	110 (77.5)	0.351
≤27, n (%)	132 (26.4)	368 (73.6)	
Mean (SD) ALT (IU/l)	27.8 (28.3)	64.2 (60.5)	<0.001
>34, n (%)	33 (9.7)	306 (90.3)	<0.001
≤34, n (%)	131 (43.2)	172 (56.8)	
HBsAg			<0.001
Positive, n (%)	34 (45.3)	41 (54.7)	
Negative, n (%)	130 (22.9)	437 (77.1)	

ALT, alanine aminotransferase; BMI, body mass index; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

the cut-off value (= 1 SCO), in this study, the anti-HCV tests were also rechecked if the data were 1–2 SCO. For avoiding false-positive tests, anti-HCV was also rechecked for the participants with positive anti-HCV and negative HCV RNA. When comparing clinical factors between 642 anti-HCV-positive participants, with and without clearance of serum HCV RNA, we found that patients with positive HBsAg had a significantly higher proportion of HCV RNA clearance than those negative for HBsAg ($p < 0.001$; table 1). In a stepwise logistic regression analysis, positive HBsAg was the only independent factor significantly associated with negative HCV RNA in anti-HCV participants (OR 0.348; 95% CI 0.211 to 0.574, $p < 0.001$). HBV carriers were observed to have a significantly higher proportion of HCV RNA clearance than non-carriers among men and women (fig 1).

Viral interferences and reciprocal viral interactions have been observed between HBV and HCV dual infection.^{7,8} Our previous study also showed that there might be a reciprocal viral interaction between HBV and HCV in patients with dual viral infection treated with interferon/ribavirin combination.⁹ Reports from Egypt and Japan^{2,3} were conducted in countries endemic for HCV where the prevalence of HBV carriers was <8% and they did not elucidate the influence the HBV infection. In our large-scale community-based study in an area endemic for HCV infection in a country hyperendemic for HBV, the important role of HBV carriers on HCV clearance was noteworthy and especially demonstrated. Besides, we did not find the effect of gender on the HCV clearance observed in previous studies.^{2,3} It seems necessary to conduct prospective, longitudinal studies in clarifying roles of gender or concurrent HBV infection on the HCV clearance rate in patients infected with HCV.

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doi: 10.1136/gut.2006.116384

Competing interests: None.

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Relation between incidence of hepatic carcinogenesis and integration value of alanine aminotransferase in patients with hepatitis C virus infection

Alanine aminotransferase (ALT) activity is the most widely used laboratory parameter in the evaluation of necroinflammatory activity in liver disease.^{1–3} However, it is incorrect to evaluate the arithmetic or the annual mean values. If the ALT level is high, the measurement interval decreases, whereas if the ALT level is low, the interval increases. As a result, the arithmetic mean value increases in patients with increased ALT levels. We performed a more accurate evaluation by using the integration value of ALT. The aim of this study was to determine the utility of the integration value of ALT in predicting hepatic carcinogenesis in patients with the hepatitis C virus (HCV) infection.

A total of 1704 consecutive patients with follow-up periods of ≥3 years, with no evidence of hepatocellular carcinoma (HCC) for ≥3 years before the observation period, and interferon treatment completed ≥3 year before the detection of HCC during the period from January 1995 to December 2002 were included. In all, 594 patients received interferon treatment and 1110 patients did not. All patients were followed up at Ogaki Municipal Hospital, Ogaki, Japan, at least every 6 months. During each follow-up examination, liver-function tests, including ALT, were measured. We calculated the area of a trapezoid with ALT value and the measurement interval, and added the values. We divided the integration value of ALT by the observation period to obtain the average integration value. Patients were classified into five groups according to the average integration value of ALT: group A, 0–20 IU/l (n = 217); group B, 21–40 IU/l (n = 614); group C, 41–60 IU/l (n = 446); group D, 61–80 IU/l (n = 240); and group E, ≥81 IU/l (n = 187). The median (range) follow-up period was 7.9 (3.0–16.8) years. The total number of blood examinations was 90 211, and the median (range) number of blood examinations was 33 (6–222). Factors associated with the cumulative incidence of HCC were analysed using the Cox proportional hazard model with the forward selection method.

HCC occurred in 206 of 1704 (12.1%) patients during the follow-up period. According to univariate analysis, the following were significantly associated with the development of HCC:

- Age >65 years (relative risk (RR) 2.688 (95% CI 2.020 to 3.578); $p < 0.001$);

Table 1 Factors associated with hepatocarcinogenesis (multivariate analysis)

	RR (95% CI)	p Value
Age (years)		
≤65	1	<0.001
>65	1.964 (1.436 to 2.685)	
Sex		
F	1	0.001
M	1.675 (1.242 to 2.259)	
Average integration value of ALT (IU/l)		
0–20	1	<0.001
21–40	3.845 (1.117 to 13.298)	0.033
41–60	4.050 (1.206 to 13.597)	0.024
61–80	9.125 (2.789 to 29.857)	<0.001
≥81	18.838 (5.735 to 61.881)	<0.001
Platelets ($\times 10^4/\text{mm}^3$)		
≥12.0	1	<0.001
<12.0	3.277 (2.435 to 4.409)	
ALP (IU/l)		
≤338	1	0.003
>338	1.590 (1.167 to 2.166)	
Cholinesterase (IU/l)		
≥431	1	0.006
<431	7.856 (1.824 to 33.830)	
Albumin (g/dl)		
≥3.5	1	<0.001
<3.5	2.901 (1.973 to 4.266)	
IFN treatment		
No treatment	1	0.015
Non-SVR	0.891 (0.429 to 1.851)	0.395
SVR	0.537 (0.349 to 0.827)	0.005

ALP, alkaline phosphatase; ALT, alanine aminotransferase; F, female; IFN, interferon; M, male; SVR, sustained virologic response.

- Male sex (1.515 (1.138 to 2.018); $p = 0.004$);
- HCV genotype 2 (1.452 (1.003 to 2.102); $p = 0.048$);

Figure 1 Incidence of hepatocarcinogenesis according to the average integration value of alanine aminotransferase (ALT). Patients were classified into five groups according to the average integration value of ALT: group A, 0–20 IU/l; group B, 21–40 IU/l; group C, 41–60 IU/l; group D, 61–80 IU/l and; group E, ≥81 IU/l. With the exception of group B vs group C, group C vs group D and group D vs group E, the cumulative incidence of hepatic carcinogenesis differed significantly between the five groups ($p = 0.0020$ to <0.001).

- High average integration value of ALT (group B (4.977 (1.541 to 16.075); $p < 0.001$); group C (8.598 (2.690 to 27.486); $p < 0.001$); group D (14.989 (4.674 to 48.062); $p < 0.001$); group E (25.358 (7.940 to 80.985); $p < 0.001$), fig 1);
- High aspartate aminotransferase level >40 IU/ml (3.283 (2.272 to 4.745); $p < 0.001$), low platelet count $<12.0 \times 10^4/\text{mm}^3$ (5.214 (3.953 to 6.877); $p < 0.001$);
- Low prothrombin time level $\leq 70\%$ (2.575 (1.760 to 3.768); $p < 0.001$);
- High γ glutamyl transpeptidase level >56 IU/ml (2.615 (1.990 to 3.438); $p < 0.001$);
- High total bilirubin level >1.2 mg/dl (1.990 (1.279 to 3.098); $p = 0.002$);
- High alkaline phosphatase level >338 IU/ml (3.126 (4.604 to 74.783); $p < 0.001$);
- Low cholinesterase level <431 IU/ml (18.555 (4.604 to 79.783); $p < 0.001$);
- High total protein level ≥ 6.5 g/dl (1.775 (1.065 to 2.958); $p < 0.001$);
- Low albumin level <3.5 g/dl (4.881 (3.341 to 6.945); $p < 0.001$);
- Low total cholesterol level <130 mg/dl (11.925 (1.671 to 85.085); $p < 0.001$);
- Type of response to IFN treatment (sustained virologic response, 0.142 (0.074 to 0.273) $p < 0.001$; non-sustained virologic response, 0.403 (0.260 to 0.601); $p < 0.001$).

According to multivariate analysis, increasing age, male sex, low platelet count, high

average integration value of ALT, low cholinesterase level, low albumin and type of response to interferon treatment were significantly associated with the incidence of HCC as shown in table 1.

We showed that increased liver inflammation, as assessed by increased ALT level, is associated with increased risk for development of HCC in patients with HCV infection.^{4–6} The average integration value of ALT, even within the current normal range, was strongly associated with the cumulative incidence of hepatocarcinogenesis. Inhibition of ALT to a value as low as possible is necessary for the prevention of hepatic carcinogenesis.

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doi: 10.1136/gut.2006.118455

Competing interests: None.

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BOOK REVIEWS

Upper Gastrointestinal Surgery

Edited by Fielding JW, Hallisey MT, Lumley J. Published by Springer, Berlin, 2005, £115.50 (hardback), pp 396. ISBN 1852336072

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