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Research Article

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Data mining model using simple and readily available factors could identify patients at high risk for hepatocellular carcinoma in chronic hepatitis C

Masayuki Kurosaki[1], Naoki Hiramatsu[2], Minoru Sakamoto[3], Yoshiyuki Suzuki[4], Manabu Iwasaki[5], Akihiro Tamori[6], Kentaro Matsuura[7], Sei Kakinuma[8], Fuminaka Sugauchi[9], Naoya Sakamoto[8], Mina Nakagawa[8], Namiki Izumi[1,*]

[1]*Division of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Tokyo, Japan;* [2]*Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Osaka, Japan;* [3]*First Department of Internal Medicine, University of Yamanashi, Yamanashi, Japan;* [4]*Department of Hepatology, Toranomon Hospital, Tokyo, Japan;* [5]*Department of Computer and Information Science, Seikei University, Tokyo, Japan;* [6]*Department of Hepatology, Osaka City University Medical School, Osaka, Japan;* [7]*Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan;* [8]*Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University, Tokyo, Japan;* [9]*Department of Gastroenterology, Nagoya Koseiin Medical Welfare Center, Nagoya, Japan*

Background & Aims: Assessment of the risk of hepatocellular carcinoma (HCC) development is essential for formulating personalized surveillance or antiviral treatment plan for chronic hepatitis C. We aimed to build a simple model for the identification of patients at high risk of developing HCC.

Methods: Chronic hepatitis C patients followed for at least 5 years (n = 1003) were analyzed by data mining to build a predictive model for HCC development. The model was externally validated using a cohort of 1072 patients (472 with sustained virological response (SVR) and 600 with nonSVR to PEG-interferon plus ribavirin therapy).

Results: On the basis of factors such as age, platelet, albumin, and aspartate aminotransferase, the HCC risk prediction model identified subgroups with high-, intermediate-, and low-risk of HCC with a 5-year HCC development rate of 20.9%, 6.3–7.3%, and 0–1.5%, respectively. The reproducibility of the model was confirmed through external validation ($r^2 = 0.981$). The 10-year HCC development rate was also significantly higher in the high- and intermediate-risk group than in the low-risk group (24.5% *vs.* 4.8%; $p < 0.0001$). In the high-and intermediate-risk group, the incidence of HCC development was significantly reduced in patients with SVR compared to those with nonSVR (5-year rate, 9.5% *vs.* 4.5%; $p = 0.040$).

Conclusions: The HCC risk prediction model uses simple and readily available factors and identifies patients at a high risk of HCC development. The model allows physicians to identify patients requiring HCC surveillance and those who benefit from IFN therapy to prevent HCC.

Keywords: Decision tree; Prediction; Pegylated interferon; Ribavirin; Risk.
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* Corresponding author. Address: Division of Gastroenterology and Hepatology, Musashino Red Cross Hospital, 1-26-1 Kyonan-cho, Musashino-shi, Tokyo 180-8610, Japan. Tel.: +81 422 32 3111; fax: +81 422 32 9551.
E-mail address: nizumi@musashino.jrc.or.jp (N. Izumi).

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide [1] and its incidence is increasing in many countries [2]. Chronic viral hepatitis is responsible for 80% of all HCC cases [2]. The need to conduct HCC surveillance should be determined according to the risk of HCC development because this surveillance is cost-effective only in populations with an annualized cancer development rate of ⩾1.5% [3]. The annualized rate of developing HCC from type C liver cirrhosis is 2–8% [4–6], indicating that this population with type C liver cirrhosis needs surveillance. However, the annualized rate of HCC development is <1.5% in patients with chronic hepatitis C but without cirrhosis and the benefit of surveillance for all patients with chronic hepatitis has not yet been established [3]. HCC surveillance may be needed for patients with advanced fibrosis because the risk of HCC development increases in parallel with the progression of liver fibrosis [7,8]. Liver biopsy is the most accurate means of diagnosing fibrosis, but a single liver biopsy cannot indicate long-term prognosis because liver fibrosis progresses over time. Serial liver biopsies are not feasible because of the procedure's invasiveness. Moreover, factors other than fibrosis, such as advanced age, obesity, sex, lower albumin, and low platelet counts, also contribute to the development of HCC from chronic hepatitis C [8–11]. Therefore, these factors must be considered while assessing the risk of HCC development.

A meta-analysis of controlled trials [12] has shown that interferon (IFN) therapy reduced the rate of HCC development in patients with type C liver cirrhosis. However, there was a marked heterogeneity in the magnitude of the prevention effect

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of IFN on HCC development among the studies, probably due to the large differences in the baseline rate of HCC development among the different trials [12]. Whether the incidence of HCC development could be reduced in all patients with chronic hepatitis C, especially in those without liver cirrhosis, remains to be elucidated.

Data mining analysis, unlike conventional statistical analysis, is performed in an exploratory manner without considering a predefined hypothesis. Decision tree analysis, the major component of data mining analysis, is used to extract relevant factors from among various factors. These relevant factors are then combined in an orderly sequence to identify rules for predicting the incidence of the target outcome [13]. Data mining analysis has been used to define prognostic factors in various diseases [14–20]. In the field of hepatic diseases, data mining analysis has proven to be a useful tool for predicting early response [21], sustained virological response (SVR) [22–25], relapse [26], and adverse events [27] in patients with chronic hepatitis C treated with pegylated interferon (PEG-IFN) plus ribavirin (RBV). The findings of data mining analysis are expressed as flowcharts and are therefore easily understood [28] and readily available for clinical use, even by physicians without a detailed understanding of statistics.

In the present study, data mining analysis was used to identify risk factors for HCC development in a cohort of patients with chronic hepatitis C who had been followed for at least 5 years. An HCC risk prediction model was constructed on the basis of simple and generally available tests because the goal was to make the model easy to use in the clinic. The suitability, reproducibility, and generalizability of the results were validated using the data of an external cohort that was independent of the model derivation cohort.

Materials and methods

Patients

The model derivation cohort consisted of 1003 chronic hepatitis C patients without cirrhosis who had a non-sustained virological response (nonSVR) to previous IFN administered at the Musashino Red Cross Hospital and were followed for at least 5 years. Patients who had SVR or those who were followed for less than 5 years were not included. An analytical database on age, body mass index, albumin, aspartate aminotransferase (AST) levels, alanine aminotransferase (ALT) levels, γ-glutamyltransferase (GGT) levels, total bilirubin levels, total cholesterol levels, hemoglobin levels, and platelet count at the start of the observation was created. Histological data such as fibrosis stage, activity grade, or degree of steatosis was not included in the database because the goal of the present study was to make the model on the basis of simple and generally available tests. The patients who developed HCC more than 5 years after the start of the observation were considered not to have developed HCC by the 5-year point because the model was intended to predict HCC development within 5 years. The 1072 chronic hepatitis C patients included in the external validation cohort were treated with PEG-IFN and RBV at the University of Yamanashi, Tokyo Medical and Dental University, Osaka University, Osaka City University, Nagoya City University, or Toranomon Hospital and followed for at least 5 years. Among them, 600 had nonSVR and 472 had SVR. Data from nonSVR patients in this external cohort were used for external validation of the HCC prediction model. To assess the preventive effect of PEG-IFN plus RBV therapy on HCC development, the cumulative HCC development rate was compared between SVR and nonSVR patients in the external validation cohort after stratification by the risk of HCC development as determined by data mining analysis. Informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review committees of all concerned hospitals.

HCC surveillance and diagnosis

HCC surveillance was conducted by performing abdominal ultrasonography every 4–6 months. Contrast-enhanced computer tomography, magnetic resonance imaging, or angiography were performed when abdominal ultrasonography suggested a new lesion suspicious for HCC. Classical HCC was diagnosed for tumors showing vascular enhancement with washout on at least two types of diagnostic imaging. Tumor biopsy was used to diagnose tumors with non-classical imaging findings.

Statistical analysis

The IBM-SPSS Modeler 13 (IBM SPSS Inc., Chicago, IL, USA) was used for decision tree analysis. The statistical methods used have been described previously [21,22,24–27]. In brief, the software searched the analytical database for the factor that most effectively predicted HCC development and for its cutoff value. The patients were divided into two groups according to that predictor. Each divided group was repeatedly assessed and divided according to this 2-choice branching method. Branching was stopped when the number of patients decreased to $\leqslant 20$ to avoid over fitting. Finally, an HCC risk prediction model was created through this analysis. The model classified patients into subgroups with different HCC development rates in a flowchart form. For model validation, nonSVR patients from an external cohort were individually fitted into the model and classified into the subgroups and the HCC development rates of those subgroups were then calculated. The suitability and reproducibility of the model were validated by comparing the subgroup HCC development rates of the model derivation group to those of the validation group.

On univariate analysis, Student's *t*-test was used for continuous variables and Fisher's exact test was used for categorical data. Logistic regression was used for multivariate analysis. A log-rank test for Kaplan–Meier analysis was used to statistically test HCC development rates over time. *p*-Values of <0.05 were considered significant. SPSS Statistics 18 (IBM SPSS Inc.) was used for these analyses.

Results

Univariate and multivariate analysis of factors associated with HCC development

The baseline characteristics of patients are shown in Table 1. The 5-year HCC development rate in the model derivation group was 6.2%, which did not differ significantly from the rate of 6.0% in the nonSVR group of the external cohort, but the rate of 2.0% in the SVR group of the external cohort was significantly lower than that in the model derivation group ($p = 0.0003$) and the nonSVR group of the external cohort ($p = 0.0012$). On univariate analysis, the factors found to be associated with HCC development in the model derivation cohort were age, AST levels, albumin levels, total cholesterol levels, and platelet count. On multivariate analysis, age (odds ratio 1.086), albumin levels (odds ratio 0.248), and platelet count (odds ratio 0.842) were significant predictors of HCC development (Table 2).

HCC risk prediction model by data mining analysis

The results of decision tree analysis are presented in Fig. 1. Age was selected as the first predictor. The 5-year HCC development rate was 3.4% in younger patients (<60 years) and 8.6% in older patients ($\geqslant$60 years). The second predictor for younger patients (<60 years) was platelet count. The HCC development rate was 6.9% in patients with a lower platelet count ($<150 \times 10^9$/L) and 0.8% in patients with a higher count ($\geqslant 150 \times 10^9$/L). The second predictor for older patients ($\geqslant$60 years) was also platelet count. The HCC development rate was 13.1% in patients with a lower platelet count ($<150 \times 10^9$/L) and 1.8% in patients with a higher count ($\geqslant 150 \times 10^9$/L). The third predictor was albumin levels,

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Table 1. Baseline characteristics of patients for model deviation and external validation.

	Model derivation (n = 1003)	External cohort, non-SVR (n = 600)	External cohort, SVR (n = 472)
Sex: Male/Female*	463 (46%)/540 (54%)	306 (51%)/294 (49%)	299 (63%)/173 (37%)
Age (yr)	57.3 (11.1)	55.9 (9.6)	51.4 (10.6)
Body mass index (kg/m^2)	23.5 (3.2)	23.4 (3.3)	23.3 (3.1)
Albumin (g/dl)	4.1 (0.3)	4.0 (0.4)	4.0 (0.3)
AST (IU/L)	64.2 (36.5)	67.3 (43.8)	62.5 (48.3)
ALT (IU/L)	80.6 (55.1)	81.2 (62.3)	88.6 (82.1)
GGT (IU/L)	59.3 (50.5)	67.6 (65.1)	55.7 (71.2)
Total cholesterol (mg/dl)	172.1 (31.5)	168.2 (31.0)	174.3 (33.7)
Platelet (10^9/L)	154.0 (53.0)	153.7 (53.2)	176.6 (49.7)
Hemoglobin (g/dl)	13.3 (1.5)	14.2 (1.5)	14.4 (1.4)
HCC development within 5 years: n (%)*	62 (6.2%)	36 (6.0%)	10 (2.0%)

Data expressed as mean (standard deviation) unless otherwise indicated.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma; SVR, sustained virological response.
*Data expressed as number of patients (percentage).

whose cutoff value was 3.75 g/dl in patients with a higher platelet count ($\geqslant 150 \times 10^9$/L). The HCC development rate was 6.3% when albumin levels were lower (<3.75 g/dl) and 1.5% when levels were higher ($\geqslant$3.75 g/dl). The cutoff value for albumin levels was 4.0 g/dl in patients with a lower platelet count ($<150 \times 10^9$/L). The HCC development rate was 20.9% when albumin levels were lower (<4.0 g/dl) and 6.4% when levels were higher ($\geqslant$4.0 g/dl). The fourth and final predictor was AST levels. The HCC development rate was 7.3% when AST levels were at least 40 IU/L and 0% when the levels were <40 IU/L. On the basis of this analysis, seven subgroups with a 5-year HCC development rate of 0–20.9% were identified. The area under the receiver operating characteristic curve according to the HCC risk prediction model was 0.817.

External validation of the HCC risk prediction model with an independent external cohort

Six hundred nonSVR patients from an external cohort were fitted into the HCC risk prediction model and classified into the seven subgroups. The 5-year HCC development rate of these subgroups was 0–17.9%. The HCC development rate in the individual subgroups of the model derivation group was closely correlated to that in the corresponding subgroups of the external validation group (Fig. 2; correlation coefficient $r^2 = 0.981$). The HCC development rate in the subgroup of patients with the highest risk of HCC development (high-risk group) according to the model older age ($\geqslant$60 years) with a lower platelet count ($<150 \times 10^9$/L) and lower albumin levels (<4.0 g/dl) was 20.9% in the model derivation group and 17.9% in the external validation group. The intermediate-risk group or the patients with an HCC development rate of at least 5% consisted of the following three subgroups: (1) older age ($\geqslant$60 years), lower platelet count ($<150 \times 10^9$/L), higher albumin levels ($\geqslant$4.0 g/dl), and higher AST levels ($\geqslant$40 IU/L); (2) older age ($\geqslant$60 years), higher platelet count ($\geqslant 150 \times 10^9$/L), and lower albumin levels (<3.75 g/dl); and (3) younger age (<60 years) and lower platelet count ($<150 \times 10^9$/L). In these intermediate-risk groups, the 5-year HCC development rate was 6.3–7.3% in the model derivation group and 5.3–7.9% in the external validation group. The low-risk group consisted of the following three subgroups: (1) younger age (<60 years) and higher platelet count ($\geqslant 150 \times 10^9$/L); (2) older age ($\geqslant$60 years), lower platelet count ($<150 \times 10^9$/L), higher albumin levels ($\geqslant$4.0 g/dl), and lower AST levels (<40 IU/L); and (3) older age ($\geqslant$60 years), higher platelet count ($\geqslant 150 \times 10^9$/L), and higher albumin levels ($\geqslant$3.75 g/dl). In these low-risk groups, the 5-year HCC development rate was 0–1.5% in the model derivation group and 0–2.9% in the external validation group.

Table 2. Multivariable analysis of factors associated with subsequent development of HCC within 5 years.

	Odds ratio	95% CI	*p* value
Age	1.086	1.029-1.146	0.003
Albumin	0.248	0.100-0.613	0.003
Platelet	0.842	0.769-0.921	<0.0001

CI, confidence interval.

Predictability of the HCC risk prediction model on HCC development rate beyond 5 years

Cumulative HCC development rates in the high-, intermediate-, and low-risk groups were compared over time using the Kaplan–Meier method. The 10-year rates were 28.9% in the high-risk group, 22.9% in the intermediate-risk group, and 4.8% in the low-risk group (Fig. 3A). The high and intermediate-risk group created by pooling data from the high- and intermediate-risk groups had a significantly higher cumulative HCC development rate than the low-risk group beyond 5 years (Fig. 3B; 5-year rate, 11.6% *vs.* 1.0%; 10-year rate, 24.5% *vs.* 4.8%; $p < 0.0001$).

Effect of response to PEG-IFN plus RBV therapy in the reduction of HCC development: analysis stratified by the HCC risk prediction model

The 600 nonSVR patients and 472 SVR patients in the external cohort were fitted into the HCC risk prediction model and

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Research Article

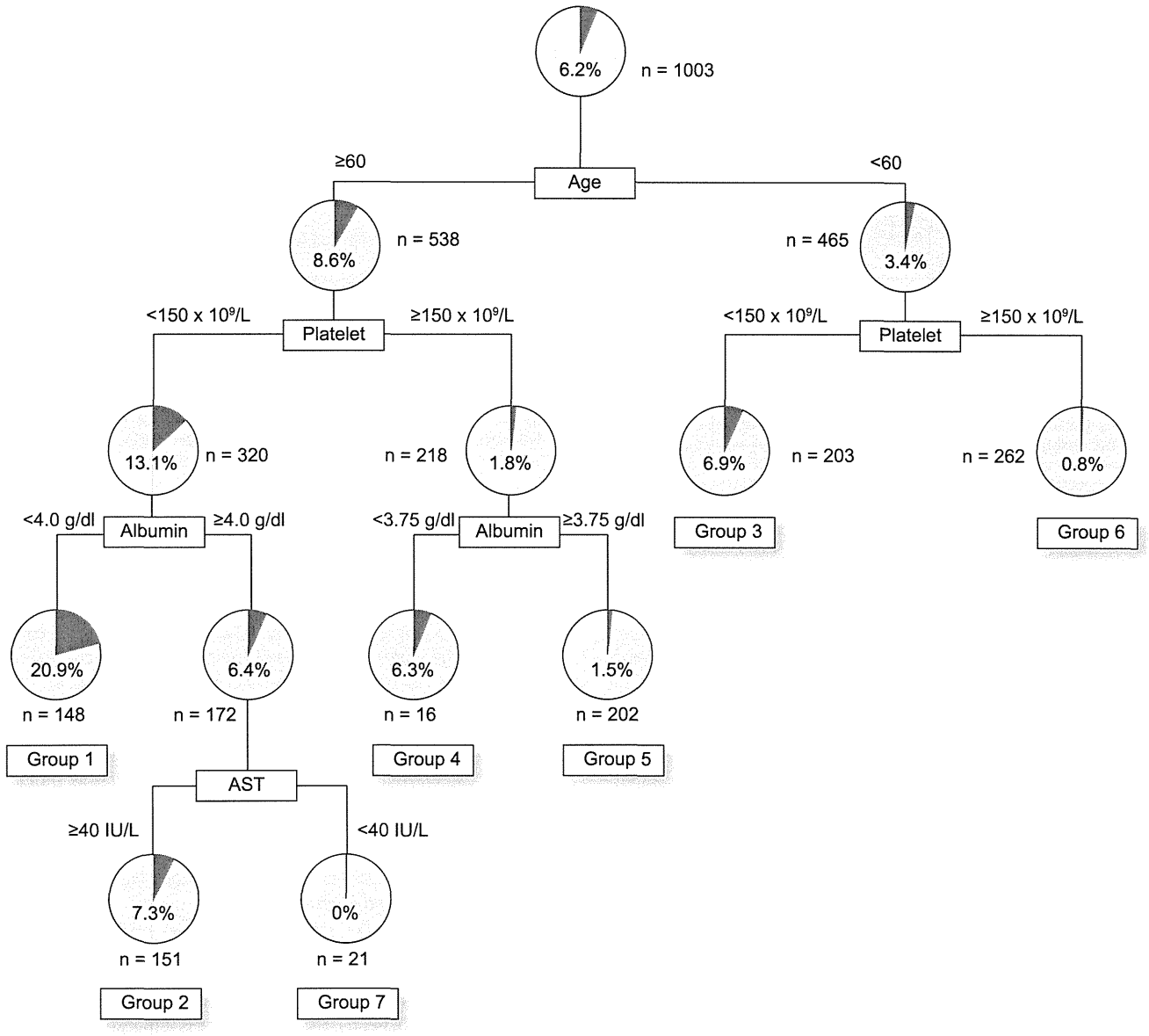

Fig. 1. The decision tree model of HCC development within 5 years. Boxes indicate the factors used to differentiate patients and the cutoff values for those different groups. Pie charts indicate the HCC development rate within 5 years for each group of patients after differentiation. Terminal groups of patients differentiated by analysis are numbered from 1 to 7.

classified into the high-and intermediate-risk group or the low-risk group, as defined above. The HCC development rate was significantly lower in SVR patients than in nonSVR patients in the high-and intermediate-risk group (5-year HCC rate, 9.5% *vs.* 4.5%; $p = 0.040$, log-rank test). In the low-risk group, the 5-year rate was 1.8% in nonSVR patients and 0.9% in SVR patients. Both rates were low and not significantly different ($p = 0.331$, log-rank test) (Fig. 4).

Discussion

An awareness of the risk of HCC development in the context of routine care for chronic hepatitis C is essential for formulating an HCC surveillance plan personalized for individual patients. The risk of developing HCC from chronic hepatitis is lower than that from cirrhosis [7]; therefore, across-the-board surveillance for chronic hepatitis C is not recommended [3]. A method to easily determine this risk, without performing serial liver biopsies, would be extremely significant clinically. In the present study, an HCC risk prediction model that included the factors such as age, platelet count, albumin levels, and AST levels was constructed. The model was found to have excellent reproducibility when validated with an external cohort. This model could identify subgroups of chronic hepatitis C patients at high risk of HCC development; the 5-year HCC development rate for the high- and intermediate-risk groups was 11.6%, yielding an annual incidence of 2.3%. This HCC risk prediction model requires only

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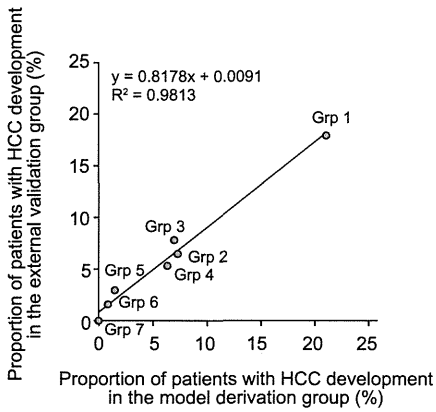

Fig. 2. External validation of the decision tree model with an independent cohort. Each patient in the external validation group was allocated to groups 1–7 following the flowchart of the decision tree. The HCC development rates were then calculated for each group and the graph plotted. The *x*-axis represents the HCC development rate in the model derivation group, and the *y*-axis represents the HCC development rate in the external validation group. The HCC development rates in each subgroup of patients are closely correlated between the model derivation group and the external validation group (correlation coefficient: $R^2 = 0.981$).

simple test values that are readily obtained in routine care and can therefore be easily used at the patient bedside. The model can be used to identify patients with a high risk of HCC development and therefore requiring surveillance, thereby allowing the formulation of surveillance plans personalized for individual patients.

Advanced fibrosis has been reported as independent risk factors for HCC development [7,8]. Platelet counts and albumin levels, which were factors selected for discrimination of the risk of HCC development, are closely related to the stage of fibrosis. Their correlation with the HCC risk has been repeatedly demonstrated [9–11,29–31]. The present study confirmed the impact of old age and advanced fibrosis, as reflected by low platelet counts and albumin levels. These results are consistent with our previous report [32]. What is unique to the present study was the study design to build a simple and reliable model for

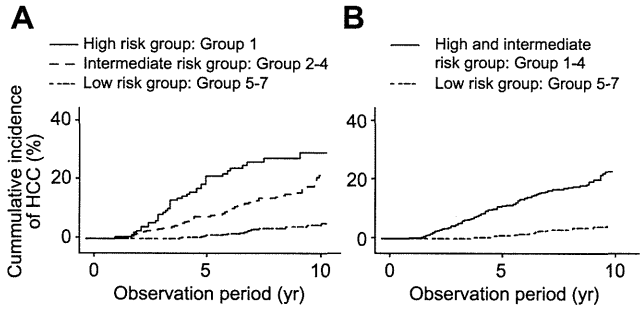

Fig. 3. Cumulative incidence of HCC development beyond 5 years in subgroups of patients defined by the decision tree model. Cumulative incidences of HCC in the groups classified by the decision tree model are compared. (A) The cumulative HCC development rate beyond 5 years is higher in the high- (group 1) and intermediate-risk (groups 2–4) groups compared to the low-risk group (groups 5–7). (B) The high and intermediate-risk group created by pooling data from the high- and intermediate-risk groups has a significantly higher cumulative HCC development rate than the low-risk group (5-year rate, 11.6% *vs.* 1.0%; 10-year rate, 24.5% *vs.* 4.8%; $p < 0.0001$).

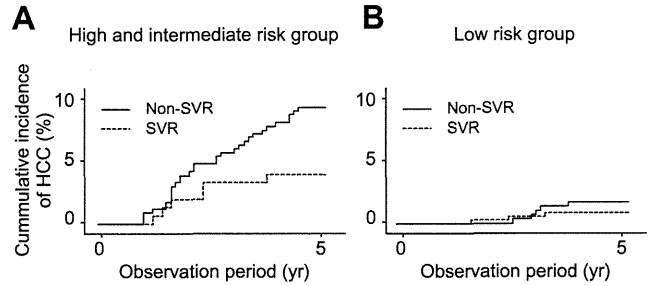

Fig. 4. Sustained virological response to PEG-IFN plus RBV therapy reduces the incidence of HCC development after stratification by the HCC risk. The 600 nonSVR patients and the 472 SVR patients in the external cohort were fitted into the HCC risk prediction model and classified into the high and intermediate-risk group or the low-risk group. The HCC development rate is significantly lower in SVR patients than in nonSVR patients in the high and intermediate-risk group (groups 1–4) (5-year HCC rate, 9.5% *vs.* 4.5%; $p = 0.040$). In the low-risk group (groups 5–7), the 5-year rate is 1.8% in nonSVR patients and 0.9% in SVR patients. Both rates are low and not significantly different ($p = 0.331$).

the prediction of HCC development that could be easily used in the clinic. For this purpose, a novel statistical method was used, histological factors were excluded in the analysis, the model derivation cohort was restricted to those who had nonSVR and had a long follow-up period duration (5 years), and the reproducibility of the model was independently validated by an external cohort. These are the major differences of the present study compared to our previous report. Many researchers have put a lot of efforts to formulate regression models for HCC prediction [9,10,33]. These prediction models are useful for identifying high-risk patients but are somewhat complicated to use at the bedside because they require calculations to be performed. Our prediction model is used simply by incorporating patients' data obtained through simple tests into the decision tree and following the flowchart. These prediction models based on factors easily accessible in routine clinical settings help physicians identify high-risk patients out of chronic hepatitis.

Viral eradication is the short-term goal of IFN therapy, but the ultimate goal is the prevention of HCC occurrence. Previous reports have shown that SVR to IFN therapy suppresses HCC occurrence in patients with type C liver cirrhosis and chronic hepatitis [7,12,30,34,35]. However, there is a marked heterogeneity in the magnitude of the treatment effect on the risk of HCC among studies, probably due to differences in the baseline risk of HCC among different trials [12]. Thus, the question remains whether the preventive effect of IFN therapy on HCC development could apply to all patients with chronic hepatitis C, especially those without liver cirrhosis. The result of the present study indicated that among high- and intermediate-risk patients, as assessed with our HCC risk prediction model, the cumulative HCC development rate was significantly reduced in SVR patients compared with nonSVR patients. This finding suggests that patients with chronic hepatitis, in whom disease has not yet progressed to hepatic cirrhosis but who are at a high risk of HCC development, benefit from antiviral treatment. The preventive effect of IFN on HCC development was not evident in low-risk patients within 5 years of observation. A longer observation term may be required to analyze the possible effect of antiviral therapy in these patients. Application of the present model on treatment decision may have limitations in that effect to prevent HCC development may differ in newer therapeutic agents such as protease

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inhibitors [36,37], and that low-risk patients may also benefit from therapy after a longer term observation period such as 15–20 years.

Patients with chronic hepatitis often have no subjective symptoms accompanying their disease and therefore have a low consciousness of the disease. The broad array of adverse reactions and the high cost of IFN therapy are frequent hurdles in motivating patients to undergo therapy. However, patients may be convinced to undergo therapy or remain motivated for continued therapy if they are made aware of their risk of HCC development and the preventive effect of IFN on HCC development.

In conclusion, a reproducible HCC risk prediction model, which includes the factors such as age, platelet count, albumin levels, and AST levels, was constructed to predict the 5-year HCC development rate in patients with chronic hepatitis C. The model requires only a combination of readily available test values and can therefore be easily used at the bedside. The information provided by the model allows the physician to identify patients requiring IFN therapy for the prevention of HCC and formulate plans for imaging HCC surveillance.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Hepatology Research

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Original Article

Impaired brain activity in cirrhotic patients with minimal hepatic encephalopathy: Evaluation by near-infrared spectroscopy

Hiroyuki Nakanishi,[1] Masayuki Kurosaki,[1] Kaoru Nakanishi,[2] Kaoru Tsuchiya,[1] Takamasa Noda,[3] Nobuharu Tamaki,[1] Yutaka Yasui,[1] Takanori Hosokawa,[1] Ken Ueda,[1] Jun Itakura,[1] Kimitaka Anami,[4] Yasuhiro Asahina,[5] Nobuyuki Enomoto,[6] Teruhiko Higuchi[3] and Namiki Izumi[1]

[1]*Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Musashino,* [2]*Department of Psychiatry, Seiwa Hospital, Shinjuku,* [3]*Department of Psychiatry, National Center of Neurology and Psychiatry, Kodaira,* [4]*Oomiyamusashino Clinic, Saitama,* [5]*Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University, Tokyo, and* [6]*First Department of Internal Medicine, Faculty of Medicine, University of Yamanashi, Chuo, Japan*

Aim: Near-infrared spectroscopy (NIRS) is a tool that could non-invasively measure the regional cerebral oxygenated hemoglobin (oxy-Hb) concentration with high time resolution. The aim of the present study is to reveal the time-dependent regional cerebral oxy-Hb concentration change coupled with brain activity during task performance in patients with minimal hepatic encephalopathy (MHE).

Methods: Cerebral oxy-Hb concentration was measured by using NIRS in 29 cirrhotic patients without overt hepatic encephalopathy (HE). Of those, 16 patients who had abnormal electroencephalography findings were defined as having MHE. Responsive increase in oxy-Hb during a word-fluency task was compared between MHE and non-MHE patients.

Results: There was no difference in the maximum value of oxy-Hb increase between patients with and without MHE (0.26 ± 0.12 vs 0.32 ± 0.22 mM·mm, $P = 0.37$). However, the pattern of the time course changes of oxy-Hb was different between the two groups. The MHE group was characterized by a gradual increase of oxy-Hb throughout the task compared to steep and repetitive increase in the non-MHE group. Increase in oxy-Hb concentration at 5 s after starting the task was significantly small in the MHE group compared to the non-MHE (0.03 ± 0.05 vs 0.11 ± 0.09 mM·mm, $P = 0.006$).

Conclusion: The cerebral oxygen concentration is poorly reactive in response to tasks among cirrhotic patients without overt HE but having abnormal electroencephalography findings. These impaired responses in regional cerebral oxy-Hb concentration may be related to the latent impairment of brain activity seen in MHE.

Key words: hepatic encephalopathy, near-infrared spectroscopy

INTRODUCTION

HEPATIC ENCEPHALOPATHY (HE) is a major complication of liver cirrhosis. Apart from clinically overt HE (OHE), minimal HE (MHE) is troublesome because it is associated with reduced quality of life (QOL), reduced cognitive function, lowered work efficiency, higher risk of progression to OHE and may be a cause of traffic accidents.[1–3] MHE treatment can improve QOL, driving capability and progression of OHE.[4–6] Adequate diagnosis of MHE and early therapeutic intervention are precluded by the lack of reliable diagnostic standards, and HE is usually diagnosed only after the presentation of overt symptoms. For the diagnosis of MHE, neuropsychological function tests, such as number connection test, light/sound reaction time, inhibitory control test, Wechsler adult intelligence scale (WAIS) or electro-psychological tests

Correspondence: Dr Namiki Izumi, Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, 1-26-1 Kyonan-cho, Musashino-shi, Tokyo 180-8610, Japan. Email: nizumi@musashino.jrc.or.jp

Conflict of interest: The authors who participated in this study have had no affiliation with the manufacturers of the drugs involved either in the past or at present, and have not received funding from the manufacturers to conduct this research.

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including electroencephalography (EEG), cerebral evoked potential, p300 event-related potential, psychometric hepatic encephalopathy score (PHES) and critical flicker test[7–15] have been employed. Diagnostic specificity can be improved by combining these tests, but complexity becomes a major disadvantage.

Recent advances in diagnostic imaging, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), made it possible to map brain function in tomographic images with high space and time resolutions. Recent study using PET[16] revealed that the primary event in the pathogenesis of OHE is inhibition of cerebral energy metabolism evidenced by reduced cerebral oxygen consumption and reduced cerebral blood flow. Whether the same mechanism could be applied to MHE is not known. Near-infrared spectroscopy (NIRS) is a tool that could non-invasively measure the cerebral blood volume as an oxygenated hemoglobin (oxy-Hb) concentration. The space and time resolution of NIRS is equivalent or higher than that of PET and fMRI. Moreover, NIRS is highly portable, does not have any restriction in the posture and flexible in setting tasks. Therefore it is possible to perform tests in a natural environment and to evaluate brain function as reflected by the dynamic changes in regional cerebral oxy-Hb concentration in response to a given task. The latter may be especially important to disclose a latent abnormality of brain function.

Recent study suggested that astrocytes regulate the cerebral blood flow and provide the oxy-Hb to the activation site of the brain.[17–19] In hepatic encephalopathy patients, function of astrocyte is impaired which may lead to cerebral oxygen consumption and blood flow.[16,20–22] We hypothesized that clinically latent abnormality of brain function in MHE also may be linked to the impairment of adequate increase in cerebral energy metabolism in response to the stimulation for activating the brain due to impaired function of astrocytes. In the present study, we used NIRS to evaluate the latent abnormality of brain function in patients with MHE, by measuring the increase of regional cerebral oxy-Hb concentration in response to task stimulation.

METHODS

Patients

A TOTAL OF 29 liver cirrhosis patients without OHE were enrolled. The underlying etiology of liver disease was hepatitis C virus infection in 19 patients, hepatitis B virus infection in two, alcoholic liver disease in five and other liver disease in three. All participants were examined by two psychiatrists to exclude mental disorders. No patient had any history of taking antidepressants or other psychotropic drugs. Subjects were examined by brain MRI or brain CT and they had no apparent brain structural disease including brain infarction. The study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of Musashino Red Cross Hospital and National Center of Neurology and Psychiatry. Informed consent was obtained from each subject. MHE was defined as those who had abnormal EEG findings. According to this definition, 16 patients were assigned to the MHE group and 13 were assigned to the non-MHE group. Table 1 shows the clinical characteristics of patients. The age and sex ratio did not differ between groups.

NIRS measurements

Concentration of oxy-Hb was measured by a 52-channel NIRS machine (Hitachi ETG4000; Hitachi Medical,

Table 1 Patient characteristics

	MHE ($n = 16$)	Non-MHE ($n = 13$)	*P*-value
Age	67.9 ± 8.9	70.1 ± 10.2	0.53
Sex (M/F)	7/9	7/6	0.72
Albumin (g/dL)	2.68 ± 0.39	3.63 ± 0.47	<0.0001
T-Bil (mg/dL)	1.83 ± 1.22	0.88 ± 0.34	0.011
PT%	64.5 ± 10.8	85.2 ± 12.7	<0.0001
Child–Pugh (A/B/C)	0/9/7	11/2/0	<0.0001
Etiology (HC/HB/Alc/Others)	8/2/4/2	11/0/1/1	0.28
NH3 (mmol/L)	90.1 ± 64.3	40.1 ± 18.3	0.012

Alc, alcoholic liver disease; HB, hepatitis B; HC, hepatitis C; MHE, minimal hepatic encephalopathy; PT%, prothrombin time percentage; T-Bil, total bilirubin.

Tokyo, Japan). NIRS detects changes in brain activity by capturing increases in regional cerebral blood flow caused by neural activity. For each channel, an optic fiber device is connected to an application probe that is placed on the subject's scalp. The 52 channels cover the frontal lobe, upper temporal lobe and anterior parietal lobe of the brain (Fig. 1). The near-infrared light penetrates the scalp and skull, passes through the brain tissue, and is partially absorbed by oxy-Hb. The reflected light is detected by a probe positioned 30 mm away from the application probe. The changes in concentration of oxy-Hb can be calculated by measuring reflected light.[23] In this study, the results measured by the seven channels which were previously reported to be diagnostic for mental disorders; (channels 36–38 and 46–49)[24–26] were selected for the analysis. The time-dependent changes in oxy-Hb concentration in each of these seven channels were compared between MHE and non-MHE patients. The sum of increase in oxy-Hb concentration in these seven channels was calculated and compared between MHE and non-MHE patients. For this analysis, increase of oxy-Hb at 5 s and maximum increase were used.

Activation task

A word-fluency task was used to stimulate frontal lobe activity. Subjects were instructed to generate as many words as possible with a given letter. For example, with a task involving "naming words starting with the letter 'T' ", subjects were given 20 s to say as many words as they could starting with the letter "T", such as "tomato", "tail" and "tea". Three tasks were presented for a total of 60 s. During the word-fluency test, the real-time changes in the oxy-Hb concentration were measured at each channel. Data are expressed as a wave form as well as in the form of topographic images.

Statistical analysis

The SPSS software package ver. 15.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. Categorical data were analyzed using Fisher's exact test. Continuous variables were compared with Student's *t*-test. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

THE NUMBER OF words generated by the word-fluency task did not differ significantly between the MHE and non-MHE groups (10.8 ± 3.4 vs 10.7 ± 2.5 words, $P = 0.93$). Figure 2 shows the time-dependent changes in the oxy-Hb concentration during the task in the representative seven channels. The average value of the seven channels (36–38 and 46–49) is shown in Figure 2. These changes reflected frontal lobe activation by the word-fluency test and correspondingly elevated cerebral blood flow in the frontal lobe. In the non-MHE

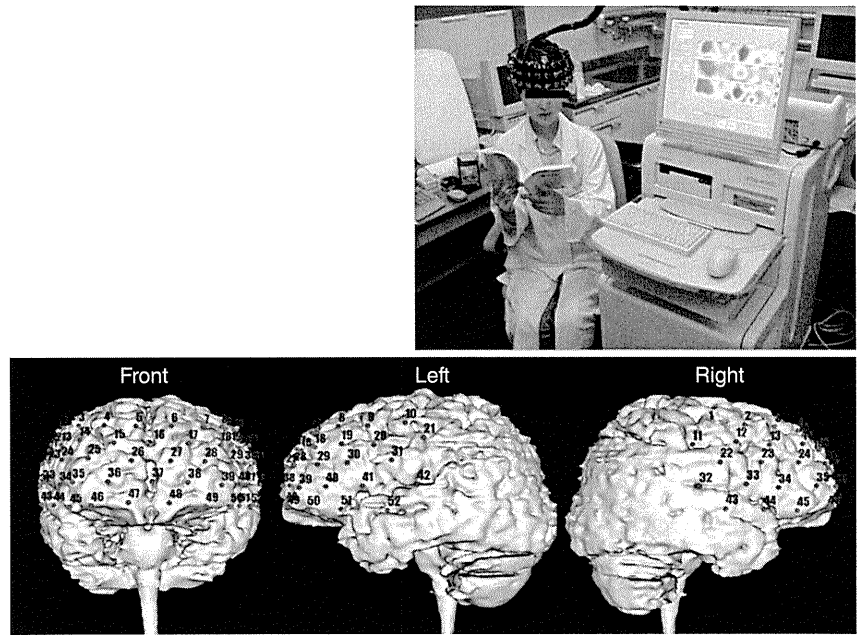

Figure 1 Near-infrared spectroscopy. An optic fiber device connected to a probe is placed on the subject's scalp covering the frontal to temporal regions. The relative concentration of oxygenated hemoglobin (oxy-Hb) was measured every 0.1 s during word-fluency testing.

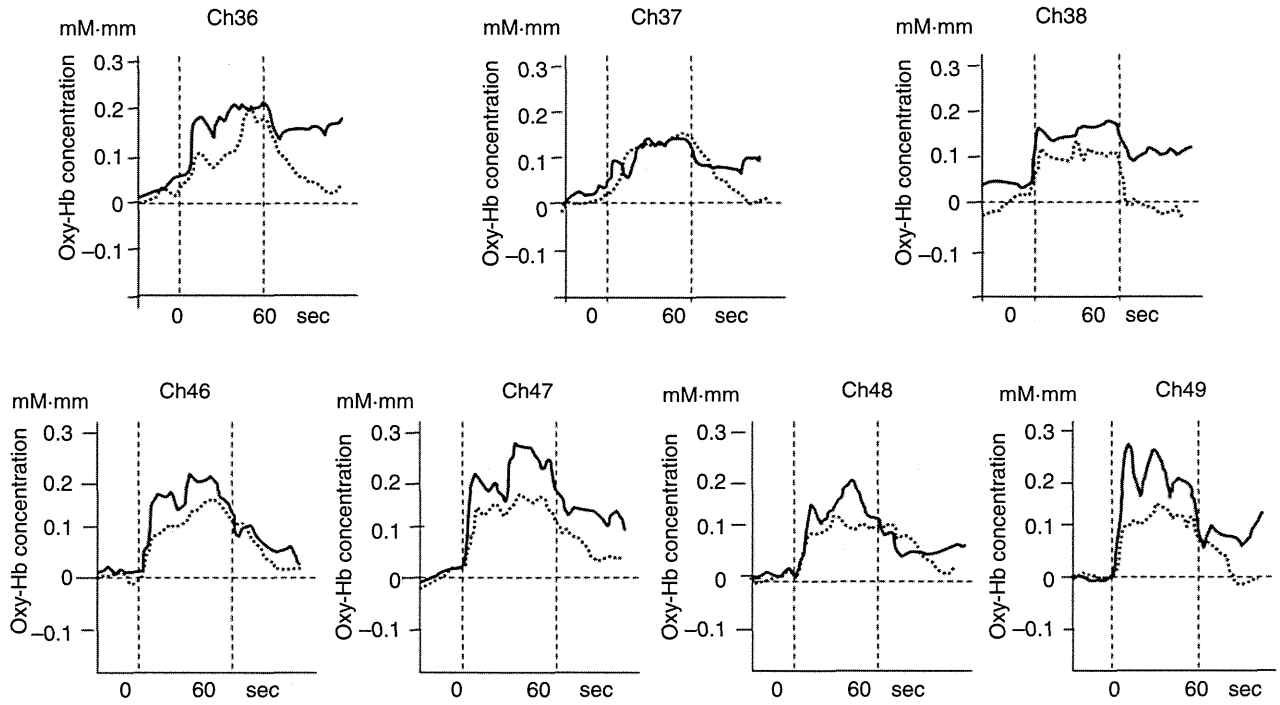

Figure 2 Time-dependent changes in oxygenated hemoglobin (oxy-Hb) concentration in response to tasks. The average waveforms of time-dependent changes in oxy-Hb concentration in representative channels (Ch) are shown. The solid and broken line represents non-minimal hepatic encephalopathy (MHE) and MHE groups, respectively. The area between the two vertical lines corresponds to the 60 s of the word-fluency test.

group, the oxy-Hb concentration increased immediately after the start of the task, remained high with repetitive steep peaks during the task, and decreased after the end of the task. In contrast, the time course of oxy-Hb changes was somewhat different in the MHE group, characterized by a slow increase of oxy-Hb throughout the task, gradually reaching a plateau at the end of the task (Fig. 2). These differences in the degree of oxy-Hb changes also could be visualized by the topographic presentation. In the topographic image, increase of oxy-Hb concentration is expressed as a deepening of the red shading. Figure 3 shows a topographic image showing the increase in oxy-Hb concentration in response to a task. The image in Figure 3 is the average value (arithmetic mean topographic image) of all patients. The concentration of oxy-Hb is small in the MHE group, as reflected by blue or green color, compared to the non-MHE group, as reflected by orange or red color.

When the average value of the seven channels were calculated, the maximum value of oxy-Hb increase was smaller in MHE compared to non-MHE patients but it did not reach statistical significance (0.26 ± 0.12 vs 0.32 ± 0.22 mM·mm, $P = 0.37$) (Fig. 4). On the other hand, increase in oxy-Hb concentration at 5 s after starting the task was significantly small in MHE compared to non-MHE patients (0.03 ± 0.05 vs

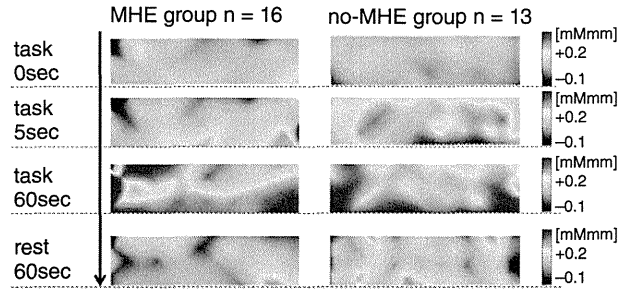

Figure 3 Topographic image showing cumulative increase in oxygenated hemoglobin (oxy-Hb) concentration. Increase in oxy-Hb concentration is shown by deepening of the red shading. The concentration of oxy-Hb is small in the minimal hepatic encephalopathy (MHE) group, as reflected by the blue or green color compared to the non-MHE group as reflected by orange or red color.

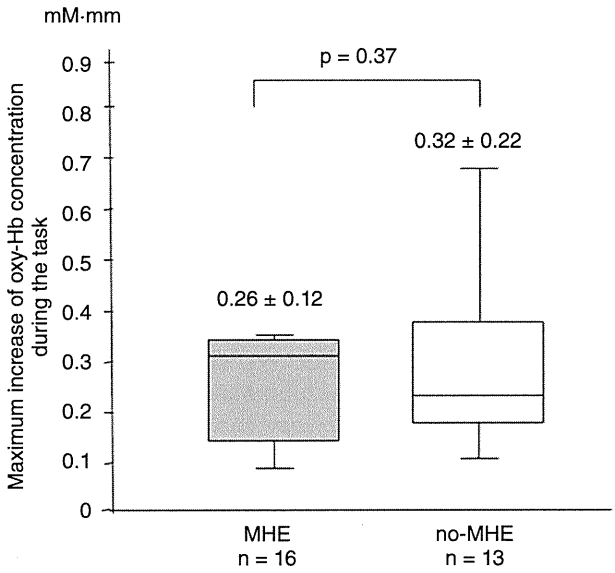

Figure 4 Comparison of maximum increase in oxygenated hemoglobin (oxy-Hb) concentration between patients with and without minimal hepatic encephalopathy (MHE). The average value of maximum increase in oxy-Hb did not differ significantly between the MHE and non-MHE groups.

0.11 ± 0.09 mM · mm, $P = 0.006$) (Fig. 5). For the diagnosis of MHE, the receiver–operator curve analysis identified an optimal cut-off of 0.05 mM · mm for the oxy-Hb concentration at 5 s after starting the task. The area under the curve was 0.774 ($P = 0.012$; 95% confidence interval, 0.60–0.95), sensitivity and specificity of NIRS for the diagnosis of MHE was 69% and 77%, respectively. The positive predictive value was 79% and negative predictive value was 67%.

DISCUSSION

USING NIRS, WHICH can detect changes in regional cerebral oxy-Hb concentration with an extremely high level of sensitivity, we found that increase in cerebral oxy-Hb concentration in response to tasks was slow and small among cirrhotic patients without OHE but having abnormal electroencephalography findings. The impairment of response was most significant at an early time point after the start of the task. These findings indicated that cerebral oxygen metabolism is poorly reactive in response to tasks among patients with MHE and that this impaired cerebral oxygen metabolism may be related to the pathogenesis of latent impairment of brain activity seen in MHE. To the best of our knowledge, our study appears to be the first evaluating MHE with NIRS. The non-invasiveness and high time resolution of NIRS give it potential as a valuable research tool for the examination of brain function in HE, as well as a clinically useful tool for the diagnosis of MHE.

Hepatic encephalopathy in its early stage, such as latent or minimal HE, can reduce cognitive function, lower work efficiency, reduce QOL[27,28] or impair driving skill.[1,2,29,30] Although there are several practical requirements for the diagnosis of MHE, adequate diagnosis of MHE is difficult due to the lack of reliable diagnostic standards.[31,32] Several diagnostic methods such as neuropsychological function tests, number connection test, light/sound reaction time, inhibitory control test, WAIS or electro-psychological tests including EEG, spectral EEG, and cerebral evoked potential, PHES, critical flicker test and computer-aided quantitative neuropsychological function test system (NP-test)[7–15] have been proposed,[32–36] but there is no ideal test for MHE as yet. Because these tests are developed for the screening of MHE, these are not diagnostic. Establishment of a reliable diagnostic method for MHE is imperative. We

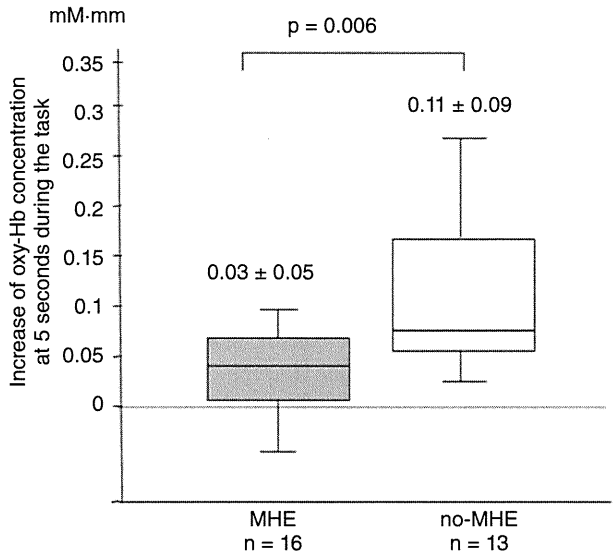

Figure 5 Comparison of increase in oxygenated hemoglobin (oxy-Hb) concentration at 5 s after the start of task between patients with and without minimal hepatic encephalopathy (MHE). The average value of increase in oxy-Hb was compared between the MHE and non-MHE groups at 5 s after starting the word-fluency task. The increase in the oxy-Hb concentration was significantly lower in patients with MHE compared to non-MHE ($P = 0.006$).

have some cases in which NIRS results improved with lactulose and branched-chain amino acid. A prospective study is ongoing to evaluate the effect of treatment by NIRS. The major advantage of NIRS over "paper and pencil tests" is the absence of learning effect which is generally seen in other neuropsychological function tests[37] and NIRS could also discriminate other mental disorders.[24,25]

Neuroimaging using MRI, magnetic resonance spectroscopy and PET has made it possible to non-invasively assess hepatic encephalopathy.[38–47] However, these tests require extensive equipment and are therefore costly. NIRS is a new methodology for brain research and brain function testing, and has applications in various areas of medicine, being used not only in research, but also in clinical medicine.[23–25,48] NIRS has been approved for identifying the language-dominant hemisphere before brain surgery and measuring epileptic foci.[49] In human studies comparing NIRS and fMRI,[50–52] a correlation was seen between blood-oxygen-level-dependent signal and oxy-Hb concentration as measured by NIRS. In brain function analysis, the detection sensitivity of NIRS is comparable to that of fMRI, but the time resolution of NIRS is greater. Furthermore, the advantages of NIRS are convenience, bedside analysis, non-invasiveness, free task setting and low cost.

Here, we used multichannel NIRS to measure the changes in oxy-Hb concentration during task performance from the frontal to temporal regions of the cortex in MHE patients and compared the results with those of liver cirrhosis without MHE. In all subjects, oxy-Hb increased during task performance and gradually decreased after the completion of task performance. However, the time-dependent changes in the degree of increase in oxy-Hb concentration differed between patients with and without MHE. The degree of increase in oxy-Hb concentration during task performance was smaller and more gradual in MHE compared to non-MHE patients. The increase of the oxy-Hb concentration reflects the increase of cerebral blood volume in the area of the brain activated by the task. Iversen *et al.* found that the cerebral oxygen consumption and blood flow were both reduced in cirrhotic patients with an acute episode of OHE[16]and that the oxygen delivery was approximately twice the oxygen consumption, indicating that oxygen delivery or blood flow was not a limiting factor for the oxygen consumption. Consequently, cerebral blood flow seems to be reduced as a result of diminished cerebral oxygen requirement during HE, and not vice versa.[16] It is reported that neuron-to-astrocyte signaling is a key mechanism in functional hyperemia,[17–19,53,54] and that function of astrocytes is impaired in hepatic encephalopathy patients.[20–22] Therefore, impaired astrocyte-mediated control of cerebral microcirculation can result in slow increase of cerebral blood flow during task performance in MHE patients. Thus, the sluggish increase in cerebral blood flow seen in MHE in the present study may reflect the impaired brain activity and dysfunction of astrocytes and impaired cerebral oxygen metabolism in these patients.

There are several limitations in the present study. The number of patients was not enough to make a comparison stratified by Child grade. We would like to analyze this important point in a future study. It may be possible that cerebral oxy-Hb may change due to aging or by the arteriosclerotic changes. In the present study, age was not related to NIRS results. All patients were examined by brain MRI or brain CT and they had no apparent brain structural disease including brain infarction. However, it was not possible to evaluate the arteriosclerotic changes. This may be another limitation of this study. Many neuropsychological function tests, such as number connection test, light/sound reaction time, inhibitory control test, WAIS or electro-psychological tests including EEG, cerebral evoked potential, p300 event-related potential, PHES and critical flicker test have been employed for the diagnosis of MHE. In Japan, Kato and colleagues established the computer-aided quantitative neuropsychological function test system called NP-test.[7] However, these tests were not simultaneously measured in the present study. Because we recognize the importance of comparing NIRS with other tests, we would like to solve this issue in future study.

In conclusion, NIRS, with its high degree of time resolution, enabled us to identify the characteristic time course of oxy-Hb concentration changes during tasks in MHE. The observations imply that cerebral oxygen supply and metabolism is poorly reactive in MHE, which may be related to the pathogenesis of latent impairment of brain activity.

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Serum HBV RNA as a possible marker of HBV replication in the liver during nucleot(s)ide analogue therapy

Masayuki Kurosaki, Kaoru Tsuchiya, Hiroyuki Nakanishi, Jun Itakura & Namiki Izumi

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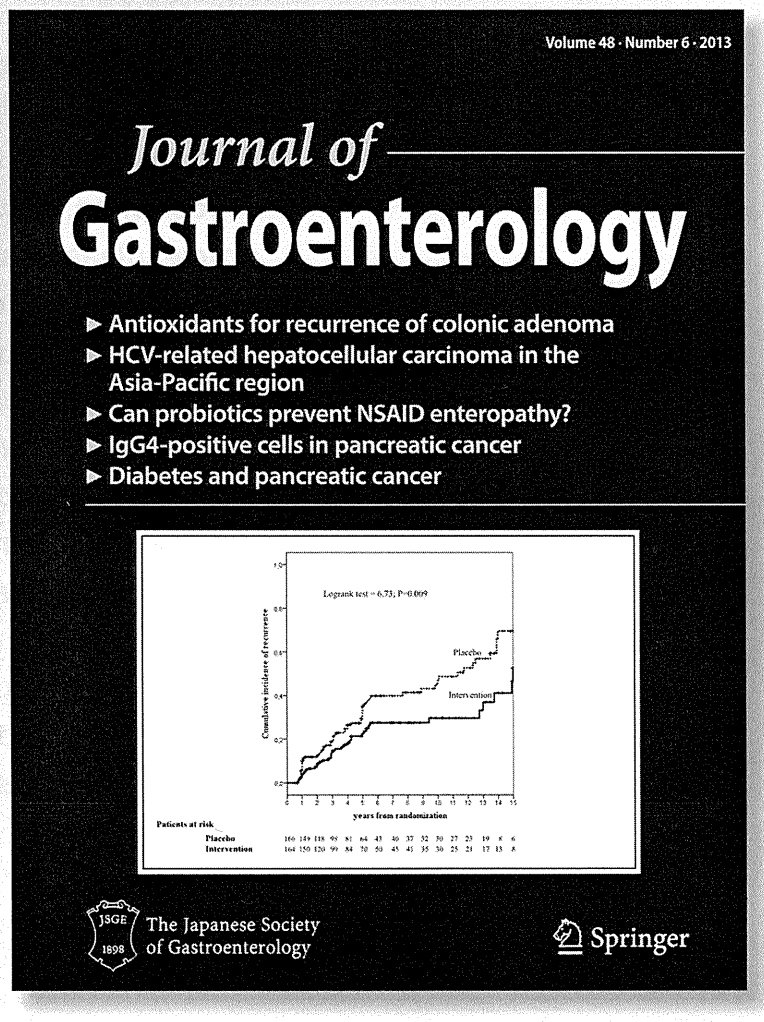

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LETTER TO THE EDITOR

Serum HBV RNA as a possible marker of HBV replication in the liver during nucleot(s)ide analogue therapy

Masayuki Kurosaki · Kaoru Tsuchiya · Hiroyuki Nakanishi · Jun Itakura · Namiki Izumi

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We read with interest the article by Tsuge et al. [1] published in the recent issue of the Journal of Gastroenterology. Treatment with nucleot(s)ide analogue (NUC) strongly suppresses the replication of hepatitis B virus (HBV) leading to a high rate of serum HBV DNA negativity. However, the incidence of relapse after the cessation of NUCs is high. Criterion for safe discontinuation of NUC therapy after long term therapy is not established to date. In HBe antigen positive patients, seroconversion, HBV DNA negativity and consolidation therapy of >6 months may be a consensus criteria but 30–50 % of patients fulfilling this criteria experience a relapse. In HBe antigen negative patients, NUC therapy is generally recommended until HBs antigen becomes undetected. Tsuge et al. [1] measured serum HBV RNA plus DNA by real time PCR and showed that the serum HBV DNA + RNA titer following 3 months of NUC treatment was a significant predictor of early (within 24 weeks) HBV DNA rebound after discontinuation of NUC. The serum HBV DNA + RNA titer was also associated with ALT rebound in HBe antigen positive patients. The results of the study by Tsuge et al. indicate that serum HBV DNA + RNA titer may serve as predictor of relapse after discontinuation of NUC.

The high rate of relapse after discontinuation of NUC is due to the persistence of HBV replication in the liver even during the NUC therapy. The replicative intermediate form of HBV, covalently closed circular DNA (cccDNA), may not be eliminated by NUC therapy and serves as a template for viral pre-genomic messenger RNA [2]. This concept was proved by a study showing that quantification of intrahepatic HBV cccDNA had a high accuracy of predicting sustained virological response after NUC discontinuation [3]. Still, we need a non-invasive and clinically usable marker for the assessment of HBV replication in the liver during NUC therapy. The measurement of HBV core related antigen may be an alternative [4]. The rationale of measuring HBV RNA in serum was that immature HBV particles including HBV RNA are released from hepatocytes during NUC treatment under the circumstances that pre-genomic HBV RNA are transcribed from HBV cccDNA, packaged into HBV core particles, but not reverse transcribed into plus-strand HBV DNA due to strong interference by NUC, and the excessive amounts of these immature particles are accumulated in hepatocytes [5, 6]. Tsuge et al. showed that serum HBV DNA + RNA titer following 3 months of NUC treatment was significantly lower in patients with no rebound of HBV DNA. By using a cut-off value of 4.8 log copies/mL, the cumulative incidence of HBV DNA rebound was significantly lower in patients with serum HBV DNA + RNA titer < 4.8 log at 3 months of NUC treatment. The same groups previously showed that HBV RNA levels at 3 months of lamivudine treatment were predictor of early emergence of resistant mutations [7]. Taken together, serum HBV DNA + RNA titer may be linked to the level of HBV replication in the liver during NUC therapy. Monitoring of serum HBV DNA + RNA response may be utilized in various decision makings in treatment of HBV patients with NUC therapy.

Based on these important findings, several questions may remain for future elucidation. Commercially available transcription-mediated amplification and hybridization assay

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M. Kurosaki (✉) · K. Tsuchiya · H. Nakanishi · J. Itakura · N. Izumi
Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, 1-26-1 Kyonan-cho, Musashino-shi, Tokyo 180-8610, Japan
e-mail: kurosaki@musashino.jrc.or.jp