Table 1 Backgrounds of 206 patients with hepatocellular carcinoma (HCC)

	e-HCC group (≥ 75 years old, $n = 63$)	Non-e HCC group (< 75 years old, $n = 143$)	*P*-value
Age (year)	78.3 ± 3.2 (range: 75 to 93)	64.2 ± 7.5 (range: 38 to 74)	< 0.001
Sex (male : female)	40:23	108:35	0.109
Frequency of positive for anti-HCV	84.1%	79.7%	0.582
Frequency of negative both for anti-HCV and HBsAg	12.7%	11.2%	0.940
Platelets ($\times 10^4$ cells/μL)	11.6 ± 6.2	11.3 ± 5.6	0.420
Alanine transferase (IU/L)	54.1 ± 23.7	71.1 ± 43.1	0.069
Albumin (g/dL)	3.7 ± 0.5	3.7 ± 0.5	0.349
Total bilirubin (mg/dL)	0.88 ± 0.51	0.88 ± 0.52	0.767
Prothrombin time (%)	81.8 ± 22.7	84.5 ± 18.3	0.553
Child-Pugh A : B	44:19	107:36	0.566
Tumor size (mm)	20.9 ± 6.1	20.7 ± 7.3	0.542
Number of tumor	1.21 ± 0.48	1.27 ± 0.57	0.101
TNM stage (I : II : III)	25:33:5	57:65:21	0.624
JIS score 0:1:2:3	15:34:14:0	46:55:36:6	0.988
Performance status (0:1)	50:13	133:10	0.009
ICG R15 (%)	27.5 ± 14.1	27.7 ± 14.4	0.886
AFP (ng/mL)	126.5 ± 533.0	143.3 ± 454.9	0.774
AFP-L3 (%)	8.3 ± 15.4	6.7 ± 13.7	0.693
PIVKA-II (mAU/mL)	676.3 ± 2643.7	142.4 ± 442.2	< 0.001
RFA with artificial pleural effusion and/or ascites	9:54	27:116	0.551
Number of laparoscopic or thoracoscopic RFA	1:62	10:133	0.178
Average observation period (days)	691.3 ± 725.0	916.0 ± 783.7	0.225

AFP, α-fetoprotein; AFP-L3, fucosylated AFP; e-HCC, elderly hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; ICG R15, indocyanine green retention rate at 15 min; JIS score, Japan Integrated Staging score; PIVKA-II, protein induced by vitamin K absence or antagonist II; RFA, radiofrequency ablation; TNM stage, tumor node metastasis stage.

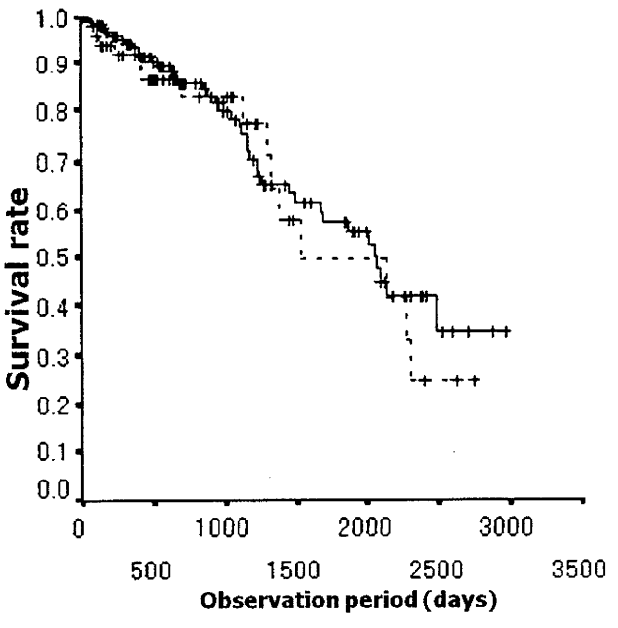

Figure 2 Survival rates of elderly hepatocellular carcinoma (HCC) group and non-elderly HCC group (total number of patients: 206). *P*-value = 0.600. — elderly HCC group ($n = 63$); — non-elderly HCC group ($n = 143$).

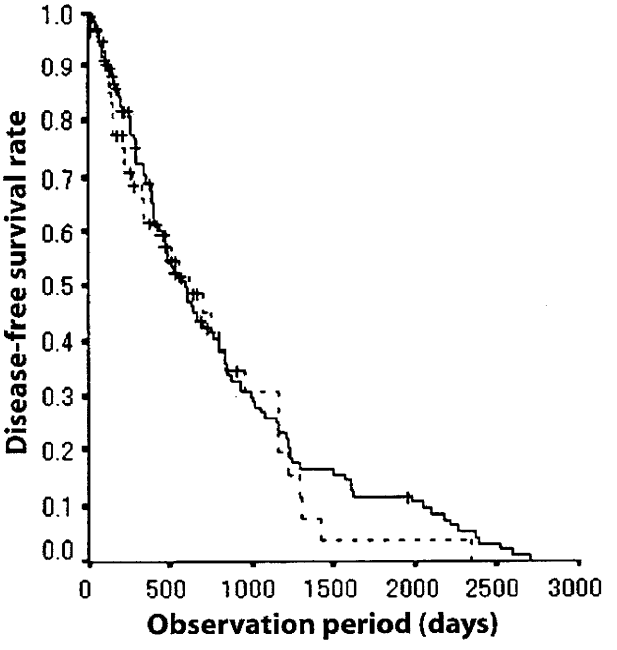

Figure 3 Disease free survival rates in the elderly hepatocellular carcinoma (HCC) group and non elderly HCC group. *P*-value = 0.454. — elderly HCC group ($n = 63$); — non-elderly HCC group ($n = 143$).

Table 2 The values for frequency of synchronous or heterochronous other malignancy

	Synchronous other malignancy	Heterochronous other malignancy
e-HCC group ($n = 63$)	Gastric cancer ($n = 1$: treated with ESD), Colon cancer ($n = 1$: treated with surgical resection)	Gastric cancer ($n = 1$: treated with ESD), Colon cancer ($n = 1$: treated with EMR)
non e-HCC group ($n = 143$)	Esophageal cancer ($n = 1$: treated with ESD), Gastric cancer ($n = 3$: treated with surgical resection or ESD), Colon cancer ($n = 1$: treated with surgical resection), Urinary bladder cancer ($n = 2$: treated with TUC or surgical resection)	Gastric cancer ($n = 1$: treated with ESD), Colonic malignant lymphoma ($n = 1$: BSC), Colon cancer ($n = 1$: treated with surgical resection), Gallbladder cancer ($n = 1$: BSC), Pancreas cancer ($n = 1$: BSC), Lung cancer ($n = 1$: BSC), Hypopharyngeal carcinoma ($n = 1$: RT), Prostate cancer ($n = 2$: treated with hormonotherapy)
P-value	$P = 0.725$	$P = 0.509$

BSC, best supportive care; e-HCC, elderly hepatocellular carcinoma; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; TUC, transurethral coagulation.

TACE have been reported as effective therapies against HCC, the strategy for elderly patients with HCC has been a big problem.

Collier described that the prognosis of elderly HCC was worse than younger HCC because of less intensive investigation and fewer patients receiving curative therapy, although the tumor stage at diagnosis was no worse in the elderly group.[24] It is important to carry out adequate investigation and follow up examination, and to carry out curative care in elderly HCC patients.

Surgical resection for elderly HCC patients has been reported to be safe and effective.[25] Yanaga reported that the mortality rate after hepatic resection was higher in elderly than younger patients.[26] Yamamoto reported that frequency of complications after resection in elderly patients was greater than in younger patients.[27] The liver reserve function is one of the important factors in selection for various therapies because most HCC patients have liver cirrhosis. In many patients whose hepatic reserve function is not adequate, invasive hepatic resection should be avoided, and less invasive therapeutic modalities should be selected. In addition, the elderly patients who are eligible for surgical resection are limited due to the complication of diseases of other organs (e.g. heart, lung, etc.), and HCC patients over 70 years old have twice the frequency of heart and lung diseases than younger patients.[26,28,29]

In elderly HCC patients, TACE[28,30] and PEIT have been reported as being just as effective as they are in younger HCC patients. Recently, RFA has become common therapy for HCC worldwide because of its low invasiveness and effectiveness. Past reports have described RFA as more effective than PEIT,[9] not to mention TACE. RFA was reported to be carried out more safely and with similar effects compared with surgical resection, though the population of liver cirrhosis with Child-Pugh B class in patients treated with RFA was larger than in patients treated with surgical resection.[14]

Teratani reported that there was no difference in mortality from extrahepatic disease between two groups separated at 70 years.[31] The frequency of other malignant diseases did not shown significant differences in the present study. In not only the non-e-HCC group but also the e-HCC group, HCC was thought to be a great factor for poor prognosis of death. In the present study, there was no significant survival rate and complications associated with RFA procedures between the e-HCC and non-e-HCC groups. Because the hepatic reserve function and TNM stage did not show significant differences between both groups, RFA was carried out with the same levels of efficacy and low invasiveness in both groups. Without the presence of other complications, such as uncontrollable advanced malignant disease or high-grade PS, RFA is considered equally effective for elderly and non-elderly HCC patients. Age was thought not to be an important factor for selecting an RFA procedure.

Elderly HCC patients, who have good performance status, should be treated in the same manner and strategy as young HCC patients.

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ORIGINAL ARTICLE

Fucosylated Fraction of Alpha-Fetoprotein as a Predictor of Prognosis in Patients with Hepatocellular Carcinoma After Curative Treatment

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Abstract
Aim The aim of this study was to evaluate the clinical usefulness of measuring the *Lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3) for prognostic predictor in patients with hepatocellular carcinoma (HCC).
Methods A total of 477 HCC patients who underwent percutaneous ablative therapy or hepatectomy were enrolled. Overall survival and recurrence-free survival were respectively evaluated retrospectively and prospectively. Multivariate analyses of clinical prognostic factors were performed by Cox's stepwise proportional hazard model.
Results AFP-L3 status was a statistically significant independent prognostic factor of long-term survival ($P = 0.013$) and recurrence-free survival ($P = 0.006$) in patients who underwent percutaneous ablative therapy. In contrast, AFP-L3 did not affect prognosis in patients who underwent hepatectomy.
Conclusions AFP-L3 had different impacts on prognosis in patients with HCC who underwent percutaneous ablative therapy and hepatectomy. Our results suggest that AFP-L3 positivity ($\geq 15\%$) might be a promising indicator for choosing therapeutic modalities in HCC patients.

Keywords Alpha-fetoprotein · AFP-L3 · DCP (des-γ-carboxy prothrombin) · Hepatocellular carcinoma · Prognostic factor

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Introduction

Hepatectomy is a generally accepted method that improves the long-term outcome in patients with hepatocellular carcinoma (HCC) [1]. However, patients with HCC frequently have coexisting liver cirrhosis with impaired hepatic functional reserve, and this may prevent surgical intervention. On the other hand, percutaneous ablative therapies, including percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT), and percutaneous radiofrequency ablation (RFA), have been developed and applied as alternative therapeutic options in cases of small HCC [2–8]. Recently, RFA has been performed as a first-line therapeutic option for early stage HCC; its survival outcomes are similar to those of hepatectomy [6–8]. However, a method for making the correct choice among therapeutic modalities to suit individual patients with early stage HCC remains to be determined.

The *Lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3) has been reported to be a specific marker for HCC [9–11]. Moreover, its level predicts the

malignant potential of HCC with subsequent unfavorable prognosis after treatment [12–16]. However, there have been few reports of the relationship between AFP-L3 status and prognosis in subgroups of HCC patients receiving different therapeutic modalities, such as hepatectomy and percutaneous ablative therapy.

The aim of this collaborative retrospective and prospective study was to evaluate the clinical usefulness of measuring AFP-L3 for prognostic predictor in patients with HCC after curative treatment.

Patients and Methods

Study Design

A total of 336 HCC patients underwent curative treatment at four participating hospitals (Niigata University Hospital, Ehime University Hospital, Shinsyu University Hospital, and Gunma University Hospital) from January 1998 to March 2005 and were investigated retrospectively. Of these patients, 232 underwent percutaneous ablative therapy and 104 underwent hepatectomy. Percutaneous ablative therapy comprised PEI in 90 patients, MCT in four patients, and RFA in 138 patients. Long-term survival data on these patients were confirmed as of the end of March 2005.

To evaluate the prognostic influence of AFP-L3 in two subgroups comparable for tumor extension, we prospectively investigated 189 patients diagnosed with early stage HCC initially at four hospitals from April 2005 to October 2007. We considered patients who had multiple (up to three) tumors measuring 3 cm or less in diameter as having early stage HCC. Forty-eight of 189 patients were excluded in this study, as they were received transcatheter treatment. As a result, 141 HCC patients, 99 who underwent percutaneous ablative therapy and 42 who underwent hepatectomy, were enrolled in the prospective study. Percutaneous ablative therapy comprised PEI in ten patients, MCT in two patients, and RFA in 87 patients. In these 141 patients, HCC recurrence was assessed by imaging modalities every 3 or 4 months after treatment and recurrence free survival was evaluated as of the end of December 2007. Informed consent was obtained from each patient, and the study protocol conformed with the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in the a priori approval by our institution's human research committee.

Diagnosis of HCC and Laboratory Examination

In our study, the diagnosis was based essentially on imaging findings together with increments of tumor marker levels. We employed methods such as computed tomography (CT), magnetic resonance imaging, and CT during hepatic arteriography, considering hyperattenuation in the arterial phase with washout in the late phase to be a typical feature of HCC. In nine cases that showed atypical features on imaging, ultrasound-guided biopsies were performed.

Hepatic functional reserve was ranked by the criteria of the Child-Pugh scoring system. Serum alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) were determined at each hospital by using commercially available kits. AFP-L3 percentage was measured at each hospital by liquid-binding assay (Wako Pure Chemical Industries Ltd, Osaka, Japan) [17]. AFP, AFP-L3, and DCP were measured in the same serum before treatment. Cut-off values for positivity for AFP, AFP-L3, and DCP were set at 20 ng/ml, 15%, and 40 mAU/ml, respectively, based on previous studies [18–20].

Treatment

Therapeutic modalities for individual patients were chosen according to hepatic functional reserve, tumor multiplicity, and tumor size. Percutaneous local ablative therapies were performed under a US-guided procedure, and its efficacy was evaluated with dynamic CT within a few days after treatment. Complete ablation of HCC was defined as non-enhancement of the lesion with surrounding liver parenchyma. Patients received additional sessions of an ablative therapy until the treatment was judged as complete. During the study, a Cool-tip RF System attached to a 200-W power generator (Radionics, Burlington, Massachusetts, USA) was the main device used for RFA treatment and Microtaze OT-110M (Alfresa-Pharma Co., Inc., Osaka, Japan) was used for MCT.

Statistical Analysis

Differences in the proportions of the independent binary variables were determined by Fisher's exact test. Continuous variables were compared by Student's *t*-test. Univariate survival and recurrence-free survival were determined by the Kaplan–Meier method. Log-rank test was used to test for equality of long-term survival and recurrence-free survival between the groups. Multivariate analyses of prognostic factors in the clinical features were performed by using Cox's stepwise proportional hazard model. The factors included for multivariate analyses were patient age, gender (female/male), HBsAg (negative/positive), Anti-HCV (negative/positive), Child-Pugh class (A/B, C), AFP (ng/ml) (<20/≥20), DCP (mAU/ml) (<40/≥40), AFP-L3 (%) (<15/≥15), tumor size (cm) (<3/≥3 or ≤2/>2), and number of tumors (single/multiple). Statistical analyses were performed with SPSS 15.0 software (SPSS Japan Inc. Tokyo, Japan). A *P*-value of less than 0.05 was considered as statistically significant.

Results

Retrospective Study

Clinical Features of Patients Classified by Therapeutic Modality

A total of 336 HCC patients who underwent hepatectomy and percutaneous ablative therapy were investigated retrospectively. Patients who underwent percutaneous ablative therapy were characterized by older age ($P < 0.05$), positivity for antibody to hepatitis C virus (anti-HCV) ($P < 0.05$), and advanced Child-Pugh classification ($P < 0.05$). In contrast, patients who underwent hepatectomy were characterized by positivity for hepatitis B surface antigen (HBsAg) ($P < 0.05$), AFP-L3 ($P < 0.05$), and DCP ($P < 0.05$) elevation, as well as large tumor size ($P < 0.05$). No significant differences were observed between the two groups in terms of gender, AFP level, or number of tumors (Table 1A).

Univariate and Multivariate Analyses of the Factors Predicting Long-Term Patient Survival

The median observation time after treatment was 38.3 months (range, 1.0–146.2 months). Of the 232 patients who underwent percutaneous ablative therapy, 172 were alive and 60 had died from HCC, hepatic failure, and/or complications of cirrhosis. Of the 104 HCC patients who underwent hepatectomy, 68 were alive and 36 had died. The median survival time was 69.0 months in patients who had undergone percutaneous ablative therapy and 114.9 months in those who had undergone hepatectomy.

In the univariate analysis, anti-HCV status ($P = 0.034$), AFP status ($P = 0.007$), AFP-L3 status ($P = 0.001$), tumor size ($P = 0.001$), and number of tumors ($P = 0.045$) were significant prognostic factors of long-term survival in patients who underwent percutaneous ablative therapy. AFP status ($P = 0.011$), tumor size ($P = 0.006$), and number of tumors ($P < 0.001$) were significant prognostic factors in patients who underwent hepatectomy (Table 2).

Multivariate analysis by Cox's stepwise proportional hazard model revealed that tumor size ($P = 0.018$) and AFP-L3 status ($P = 0.013$) were significant independent prognostic factors for long-term survival in patients who underwent percutaneous ablative therapy. Tumor size ($P = 0.013$) and number of tumors ($P = 0.004$) were significant independent prognostic factors in patients who underwent hepatectomy (Table 3). We showed the long-term survival curves of two groups (with or without AFP-L3 elevation) in patients who underwent percutaneous ablative therapy and in those who underwent hepatectomy (Fig. 1). No significant difference in survival was observed

Table 1 Clinical features of patients with HCC classified by therapeutic modality in the retrospective and prospective studies

Variables	Percutaneous ablation ($n = 232$)	Hepatectomy ($n = 104$)
(A) Retrospective study		
Age (median, range)	68 (39–89)	65 (35–81)*
Gender		
Male	145 (62.5%)	66 (63.5%)
Female	87 (37.5%)	38 (36.5%)
HBsAg		
Negative	209 (90.1%)	73 (70.2%)
Positive	23 (9.9%)	31 (29.8%)*
Anti-HCV		
Negative	28 (12.1%)	45 (43.3%)
Positive	204 (87.9%)	59 (56.7%)*
Child-Pugh class		
A	177 (76.3%)	95 (91.3%)
B and C	55 (23.7%)	9 (8.7%)*
AFP (ng/ml)		
<20	65 (28.0%)	22 (21.2%)
≥20	167 (72.0%)	82 (78.8%)
DCP (mAU/ml)		
<40	149 (67.4%)	48 (51.1%)
≥40	72 (32.6%)	46 (48.9%)*
AFP-L3 (%)		
<15	181 (78.0%)	61 (58.7%)
≥15	51 (22.0%)	43 (41.3%)*
Tumor size (cm)		
<3	185 (79.7%)	33 (31.7%)
≥3	47 (20.3%)	71 (68.3%)*
Tumor number		
Single	148 (63.8%)	75 (72.1%)
Multiple	84 (36.2%)	29 (27.9%)
Variables	Percutaneous ablation ($n = 99$)	Hepatectomy ($n = 42$)
(B) Prospective study		
Age (median, range)	69 (36–85)	65 (40–80)
Gender		
Male	66 (66.7%)	24 (57.1%)
Female	33 (33.3%)	18 (42.9%)
HBsAg		
Negative	85 (85.9%)	29 (69.0%)
Positive	14 (14.1%)	13 (31.0%)*
Anti-HCV		
Negative	27 (27.3%)	15 (35.7%)
Positive	72 (72.7%)	27 (64.3%)
Child-Pugh class		
A	79 (79.8%)	39 (92.9%)
B and C	20 (20.2%)	3 (7.1%)

Table 1 continued

Variables	Percutaneous ablation ($n = 99$)	Hepatectomy ($n = 42$)
AFP (ng/ml)		
<20	64 (64.6%)	22 (52.40%)
≥20	35 (35.4%)	20 (47.6%)
DCP (mAU/ml)		
<40	63 (63.6%)	27 (64.3%)
≥40	35 (35.4%)	15 (35.7%)
AFP-L3 (%)		
<15	85 (85.9%)	33 (78.6%)
≥15	14 (14.1%)	9 (21.4%)
Tumor size (cm)		
≤2	63 (63.6%)	27 (64.3%)
>2	36 (36.4%)	15 (35.7%)
Tumor number		
Single	78 (78.8%)	34 (81.0%)
Multiple	21 (21.2%)	8 (19.0%)

HBsAg hepatitis B surface antigen, *HCV* hepatitis C virus, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin. Percentages are shown in parentheses

* $P < 0.05$ between groups by Fisher's exact test and Student's *t*-test

between the two AFP-L3 groups in patients who underwent hepatectomy ($P = 0.308$). In contrast, patients in the ablative therapy group whose AFP-L3 levels were below 15% lived significantly longer than those whose values were more than 15% ($P = 0.001$).

Prospective Study

Clinical Features of Patients with Early Stage HCC Classified by Therapeutic Modality

A total of 141 patients with early stage HCC were evaluated prospectively. Patients who underwent hepatectomy were characterized by positive for hepatitis B surface antigen (HBsAg) ($P < 0.05$). No significant differences were observed in age, gender, anti-HCV positivity, AFP status, AFP-L3 status, DCP status tumor size, and number of tumors between the two groups. Patients who underwent percutaneous ablative therapies tended to have an advanced Child-Pugh classification ($P = 0.055$) (Table 1B).

Univariate and Multivariate Analysis of the Factors Predicting Recurrence-Free Survival in Patients with Early Stage HCC

The median follow-up time after treatment was 12.0 months (range, 1.0–30.5 months). Among the 99 patients who underwent percutaneous ablation, recurrences were observed in 36 (36.4%). Among the 42 patients who underwent hepatectomy, recurrences were observed in six (14.3%).

In the univariate analysis, we found no significant difference in recurrence-free survival rates by pretreatment variables in patients who underwent percutaneous ablation, although AFP-L3 elevation ($P = 0.054$) tended to decrease recurrence-free survival. In contrast, tumor size ($P = 0.038$) and number of tumors ($P = 0.034$) were significant prognostic factors in patients who underwent hepatectomy (Table 2).

Although this prospective study was conducted over a short period of time, multivariate analysis of prognostic factors among the clinical features was performed and Cox's stepwise proportional hazard model revealed that HBsAg status ($P = 0.033$), DCP status ($P = 0.011$), and AFP-L3 status ($P = 0.006$) were significant independent prognostic factors of recurrence-free survival in patients who underwent percutaneous ablative therapies. On the other hand, we found no significant independent prognostic factors in patients who underwent hepatectomy (Table 3).

We showed recurrence-free survival rates between two groups—with or without AFP-L3 elevation—among

Table 2 Univariate analysis of the factors predicting long-term survival in the retrospective study and recurrence-free survival in the prospective study for patients who underwent percutaneous ablation and in those who underwent hepatectomy

Variables	Long-term survival		Recurrence-free survival	
	Percutaneous ablation *P*-value	Hepatectomy *P*-value	Percutaneous ablation *P*-value	Hepatectomy *P*-value
Gender (female/male)	0.907	0.525	0.225	0.194
HBsAg (negative/positive)	0.139	0.801	0.151	0.314
Anti-HCV (negative/positive)	0.034	0.963	0.194	0.171
Child-Pugh class (A/B,C)	0.083	0.235	0.293	0.487
AFP (ng/ml) (<20/≥20)	0.007	0.011	0.117	0.994
DCP (mAU/ml) (<40/≥40)	0.328	0.153	0.075	0.059
AFP-L3 (%) (<15/≥15)	0.001	0.308	0.054	0.530
Tumor size (cm) (<3/≥3)	0.001	0.006	0.063	0.038
Tumor number (single/multiple)	0.045	<0.001	0.667	0.034

HBsAg hepatitis B surface antigen, *HCV* hepatitis C virus, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin. *P*-value was calculated using Log-rank test

Table 3 Multivariate analysis of factors predicting long-term survival in the retrospective study and recurrence-free survival in the prospective study for patients who underwent percutaneous ablation and in those who underwent hepatectomy

Long-term survival			Recurrence-free survival		
Variables	Hazard ratio (95% CI)	*P*-value	Variables	Hazard ratio (95% CI)	*P*-value
Percutaneous ablation			Percutaneous ablation		
AFP-L3 (%)			HBsAg		
<15	1		Negative	1	
≥15	2.098 (1.169–3.765)	0.013	Positive	2.823 (1.090–7.310)	0.033
Tumor size (cm)			DCP		
<3	1		<40 (mAU/ml)	1	
≥3	1.998 (1.123–3.553)	0.018	≥40 (mAU/ml)	2.767 (1.267–6.046)	0.011
			AFP-L3		
			<15 (%)	1	
			≥15 (%)	3.463 (1.437–8.347)	0.006
Hepatectomy			Hepatectomy		
Tumor size (cm)			Tumor number		
<3	1		Single	1	
≥3	6.162 (1.457–26.064)	0.013	Multiple	4.654 (0.936–23.149)	0.060
Tumor number					
Single	1				
Multiple	3.170 (1.442–6.921)	0.004			

Hazard ratio and *P*-value were calculated using Cox's stepwise proportional hazard model

CI confidence interval, *AFP* alpha-fetoprotein, *HBsAg* hepatitis B surface antigen, *DCP* des-gamma-carboxy prothrombin

patients with early stage HCC who underwent percutaneous ablation and patients who underwent hepatectomy (Fig. 1). No significant difference was observed between groups with or without AFP-L3 elevation ($P = 0.53$) in patients who underwent hepatectomy. In contrast, a close-to-significant ($P = 0.054$) difference was observed between the groups of patients with and without AFP-L3 elevation who underwent percutaneous ablative therapy.

In summary, the results of the retrospective and prospective studies demonstrated that AFP-L3 status was a statistically significant prognostic factor of long-term survival and recurrence-free survival in patients who underwent percutaneous ablative therapy, but did not affect prognosis in patients who underwent hepatectomy.

Discussion

AFP-L3, a fucosylated species of AFP, is the product of alpha 1-6 fucosyltransferase (FUT8) in the presence of GDP-fucose. Our previous result revealed that FUT8 levels in HCC tissue were higher than those in the surrounding non-cancerous tissues and that FUT8 levels of HCC tissue increased in accordance with tumor dedifferentiation [21]. Several reports have shown the relationship between AFP-L3 status and histologic grade in HCC. Miyaaki et al. [16] showed that the frequency of poorly differentiated HCC was significantly higher in AFP-L3-positive patients than in AFP-L3-negative patients. Oka et al. [14] reported that AFP-L3-positive HCC was characterized by portal vein invasion and poorer differentiation, and that tumors in AFP-L3-positive HCC were advanced, even if they were small and the patient had a low serum AFP concentration. These results indicate the relationship between increased AFP-L3 level and increased degree of malignant behavior of HCC tissue.

Recurrence after treatment is an important factor affecting prognosis. Vascular invasion is an established adverse prognostic indicator of recurrence of HCC [22, 23]. Yamashita et al. [24] suggested that portal vein invasion is associated with AFP-L3 positivity, and that there is a strong possibility of intrahepatic invasion when there is positive conversion of this marker. Hayashi et al. [13] reported the relationship between AFP-L3 status and pattern of recurrence in patients with HCC. In their report, intrahepatic metastasis was significantly more common in AFP-L3-positive patients than in negative patients, although the recurrence rate of multicentric tumors did not differ significantly between the two groups with or without AFP-L3 elevation. From this point of view, hepatectomy—especially anatomical resection, which can remove venous tumor thrombi together with the primary lesion—is more suitable than local ablative therapies for the treatment of AFP-L3-positive patients.

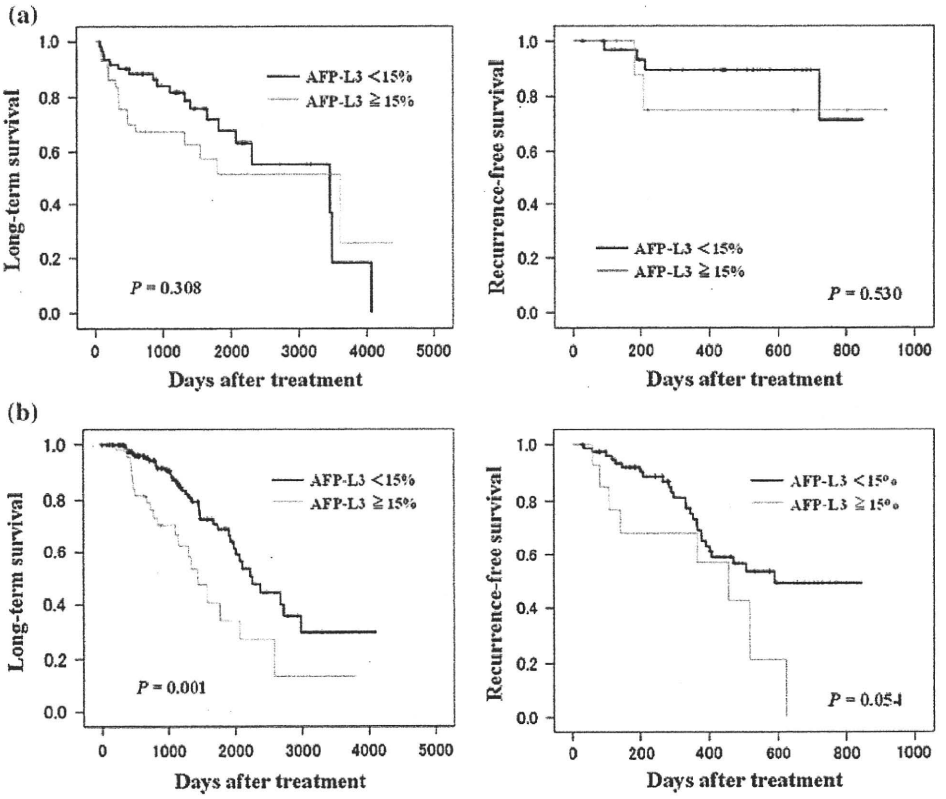

Fig. 1 Comparison of long-term survival rates and recurrence-free survival rates between patients with and without AFP-L3 elevation who underwent hepatectomy (**a**) and who underwent percutaneous ablation (**b**)

In our study, the pathological diagnosis was made by individual pathologists at each hospital. At Niigata University Hospital, 58 HCC patients underwent hepatectomy, of whom 23 had an elevated serum AFP-L3 level (≥15%) and the remaining 35 were negative for AFP-L3 (<15%). Among the 23 patients with AFP-L3 elevation, only two (8.7%) were diagnosed as having well-differentiated HCC on the basis of the resected specimens, 14 (60.9%) had moderately differentiated HCC, and seven (30.4%) had poorly differentiated HCC. In contrast, among the 35 patients who were negative for AFP-L3, 7 (20.0%) were diagnosed as having well-differentiated HCC, 24 (68.6%) had moderately differentiated HCC, and only four (11.4%) had poorly differentiated HCC. Although no statistically significant differences were observed by Fisher's exact test, the group showing AFP-L3 elevation tended to have a poorer histopathological grading ($P = 0.141$). Only eight out of 331 patients who underwent percutaneous ablative therapy were diagnosed as having HCC on the basis of histological findings in four hospitals. Therefore, we were unable to investigate whether poorly differentiated tumors were more frequent in the groups who underwent percutaneous ablative therapy and hepatectomy. Portal vein invasion was investigated similarly in 58 patients, and was found to be present in six of 23 AFP-L3-positive patients and six of 35 AFP-L3-negative patients. No significant difference was observed between AFP-L3 and portal vein invasion in this limited investigation.

We demonstrated here in a multicenter retrospective study that AFP-L3 status was a significant prognostic factor affecting the long-term survival of patients who underwent percutaneous ablative therapy. In addition, to evaluate the prognostic influence of AFP-L3 in two subgroups comparable for tumor extension, we performed a multicenter prospective study to identify the prognostic factors for recurrence-free survival in patients with early stage HCC. Although this evaluation was conducted over a short period of time, we confirmed that AFP-L3 status was a significant prognostic predictor of recurrence-free survival in patients who underwent percutaneous ablative therapy, but it did not affect the prognosis of patients who underwent hepatectomy.

A number of studies have shown that AFP-L3 status is an independent prognostic factor in patients with HCC [12, 13, 15]. We previously reported that AFP-L3-positive (>15%) patients had a lower survival rate than negative (<15%) patients in subgroups with a low serum AFP concentration. Moreover, the statistically significant differences were more distinct in the subgroups with lower AFP concentrations [20]. However, the patients in these studies had received various treatments such as hepatectomy, RFA, and transcatheter arterial embolization, and

there have been few reports of the relationship between AFP-L3 status and prognosis in subgroups of HCC patients receiving different therapeutic modalities. Tateishi et al. [15] demonstrated that pre-treatment AFP-L3 positivity (>15%) was a significant predictor of HCC recurrence in patients who underwent curative ablation, and that AFP-L3 positivity after ablation was the strongest predictor of HCC recurrence by multivariate analysis. Although their study was performed in only one center and did not evaluate long-term survival, their results are compatible with ours.

Treatment of HCC patients with cirrhosis faces a dilemma in that minimization of damage to noncancerous liver tissue improves long-term survival, but incomplete treatment of subsequent HCC recurrences results in a poor prognosis. Accordingly, if a useful indicator of choice of therapeutic modality were to be available before the initial therapy, there would be several advantages in not only the treatment, but also the follow-up, of patients with HCC.

In conclusion, present results revealed that AFP-L3 had different impacts on prognosis in patients with HCC who underwent percutaneous ablative therapy and hepatectomy. Although this study was not a randomized control trial, AFP-L3 might be a promising scale to improve the prognostic estimate and appraisal of therapeutic outcome in patients with HCC.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Etiology of liver cirrhosis in Japan: a nationwide survey

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Abstract
Background Little is understood about worldwide changes in the epidemiological distribution of the etiology of liver cirrhosis (LC). The present study examines the etiology of liver cirrhosis in Japan using a nationwide survey.
Methods We analyzed data from 33,379 patients with LC at 58 hospitals and presented the findings in a poster symposium regarding the etiology and clinical features of LC in Japan that was included in the program of the 44th Annual Meeting of the Japan Society of Hepatology. We identified the distribution of the etiology of LC and compared the present with previous Japanese findings to estimate the future of etiological changes in LC.
Results The etiological agents were as follows: hepatitis B virus (HBV) 13.9%, hepatitis C virus (HCV) 60.9%, alcohol 13.6%, primary biliary cirrhosis (PBC) 2.4% and autoimmune hepatitis (AIH) 1.9%. Cirrhosis was considered to be related to nonalcoholic steatohepatitis (NASH) in 2.1% of the patients. The ratio of HCV-related LC was significantly higher among patients with hepatocellular carcinoma (HCC) ($P < 0.0001$) compared to those without, whereas the ratios of alcohol, PBC, AIH were lower. HCC was evident in 31.5% of NASH-related LC.
Conclusions The major etiology of liver cirrhosis in Japan remains HCV. Our survey revealed the prevalence of NASH-related LC in Japan and the frequency of HCC. Future changes in etiology must be considered in establishing preventive or educational strategies, as well as in developing new treatment strategies.

Keywords Carcinogenesis · Hepatitis B virus · Hepatitis C virus · Hepatocellular carcinoma · Nonalcoholic steatohepatitis

Abbreviations

AIH	Autoimmune hepatitis
ANA	Anti-nuclear antibody
BMI	Body mass index
DM	Diabetes mellitus
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
LC	Liver cirrhosis
MetS	Metabolic syndrome

Participating investigators of The Japan Etiology of Liver Cirrhosis Study Group are listed in the Appendix.

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NAFLD Nonalcoholic fatty liver disease
NASH Nonalcoholic steatohepatitis
PBC Primary biliary cirrhosis
PSC Primary sclerosing cholangitis

Introduction

Liver cirrhosis (LC) is a life-threatening, major worldwide health problem that is defined as regenerative nodule development after chronic liver diseases. A considerable ratio of patients with LC can progress to liver failure, hepatocellular carcinoma (HCC) and portal hypertension. Chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), and alcohol consumption are the major global causes of liver cirrhosis, but the epidemiology and etiology are not well described. Alcohol and HCV are common causes of LC in European, North American and other developed countries, whereas HBV is the major cause in many Asian and African countries [1, 2]. Information about the exact ratios of LC etiology in individual areas or countries is minimal, and few Japanese reports describe analyses of large patient cohorts or nationwide surveys. Globally, about 57% of cirrhosis was attributable in 2007 to either HBV (30%) or HCV (27%) [2]. Reports indicate that alcohol is the leading cause of LC, followed by HCV in the United States of America (USA) and the United Kingdom (UK), whereas HCV is the major cause in Italy [1–5]. On the other hand, HBV is the major cause of LC in endemic areas. Liver cirrhosis of unknown causes has been referred to as cryptogenic cirrhosis, and nonalcoholic steatohepatitis (NASH) is recognized as an important cause of cryptogenic LC and/or HCC [6–9]. However, the exact prevalence of NASH-related LC is unknown.

Based on this background we analyzed the etiology and clinical features of 33,379 patients with LC from 58 hospitals nationwide and then determined accurate etiological ratios for liver cirrhosis in Japan in July 2008.

Patients and methods

Patients

A group of 58 hospitals throughout Japan responded to mailed questionnaires regarding the etiology of liver cirrhosis. The data from 33,379 patients with liver cirrhosis were presented in a poster symposium regarding the etiology and clinical features of LC at the 44th Annual Meeting of the Japan Society of Hepatology during June 2008. We included all university hospitals and other major hospitals in Japan that contribute to the care of liver diseases. The appendix lists the cooperating institutions. The ethics committees of the appropriate institutional review boards approved this study in accordance with the Declaration of Helsinki 2000.

Criteria and questionnaire

Table 1 lists the criteria for LC and the definition of etiology applied in this study. We enrolled patients who were

Table 1 Criteria for diagnosis of liver cirrhosis and classification of etiology

I. Criteria for diagnosis of liver cirrhosis

Autopsy, laparoscopy or abdominal imaging (left lobe hypertrophy with splenomegaly, nodular changes in liver surface) and laboratory findings (low platelet count, albumin, and/or prolonged prothrombin time) compatible with liver cirrhosis. Also clinically diagnosed in patients with clinical findings of esophageal varices, ascites, or hepatic encephalopathy. Patients diagnosed solely based on histological liver biopsy findings are excluded.

II. Criteria for classification of etiology

1. Hepatitis B virus (HBV): positive for HBsAg and/or anti-HBc with high titer
2. Hepatitis C virus (HCV): positive for anti-HCV and HCV-RNA
3. HBV + HCV
4. Alcohol: criteria proposed by the Japanese Study Group of Alcoholic Liver Disease
5. Primary biliary cirrhosis
6. Other biliary cirrhosis (primary sclerosing cholangitis, etc.)
7. Autoimmune hepatitis
8. Metabolic diseases (Wilson disease, hemochromatosis, etc.)
9. Congestive disease
10. Parasites
11. Other known etiology
12. Nonalcoholic steatohepatitis (NASH): fulfillment of criteria described below and not meeting any criteria for above known etiologies.
13. Unknown etiology

Table 2 Criteria for NASH-related cirrhosis

I. Clinically supposed NASH-related cirrhosis
Fulfillment of the following criteria but without liver biopsy.
1. Alcohol consumption: less than 20 g/day
2. No other etiology for liver disease
3. Combined with diseases or states that could cause fatty liver diseases such as obesity (body mass index >25), diabetes mellitus and metabolic syndrome.
II. Histologically diagnosed NASH-related cirrhosis
Fulfillment of Criteria I, and histological liver biopsy findings are suitable with NASH (micronodular cirrhosis, perisinusoidal fibrosis, fatty change).

histologically and clinically diagnosed with LC, and with LC complicated by HCC. Since consensus has not been reached regarding criteria for liver cirrhosis caused by NASH, we tentatively established the criteria shown in Table 2. Final diagnosis of LC and diagnosis of etiology was determined in each institution. We also collected clinical information (age, gender, body mass index, complicating diseases and laboratory data) about patients with LC related to NASH or of unknown etiology. Alcoholic LC was diagnosed according to the criteria proposed by Takada et al. [10]. The time of diagnosis was not restricted in this retrospective study.

Statistical analyses

Data were statistically analyzed by the χ^2 test and by Student's t test using SPSS version 13.0J software (SPSS, Inc., Tokyo, Japan). All statistical tests were two-sided. P values below 0.05 were considered significant.

Results

Etiology of liver cirrhosis

Of the 33,379 patients with LC included in this study, 20,817 (62.4%) were male, 12,562 (37.6%) were female and 16,117 overall (48.3%) had HCC at the time of diagnosis with LC.

Figure 1 compares the etiology with previous Japanese data. The present study found the following causes of LC: HCV 60.9%, HBV 13.9%, alcohol 13.6%, PBC 2.4%, NASH-related 2.1% and AIH 1.9%. Among the remaining 4.0% of patients, other known and unknown etiologies were identified in 1.0 and 3.0%, respectively. Other known etiologies comprised: other biliary cirrhosis 0.3%, congestive cirrhosis 0.3% and parasites 0.1%. Other biliary cirrhosis ($n = 104$ patients) comprised primary sclerosing cholangitis (PSC; $n = 66$), congenital biliary atresia ($n = 16$), and others ($n = 22$). Metabolic diseases ($n = 91$) comprised Wilson's disease ($n = 55$), hemochromatosis ($n = 24$), glycogen storage disease ($n = 5$), citrunemia ($n = 3$), porphyria ($n = 3$) and amyloidosis ($n = 1$).

The results show that hepatitis virus, particularly HCV, remains a major cause of liver cirrhosis in Japan. On the other hand, the incidences of HBV and of alcohol-induced LC are decreasing. We focused on NASH-related LC for this analysis, and speculated that NASH represents a major unrecognized etiology. Data from 1998 show total values for LC excluding HBV, HCV and alcohol, of 8.8%, compared with the current value of 9.9%. Thus, NASH seemed to have historically been categorized as liver cirrhosis of unknown etiology.

Geographic differences in Japan

Figure 2 shows the geographic distribution of the etiology of liver cirrhosis in Japan. The most prevalent source in almost all areas in Japan except Okinawa was HCV. Alcohol was the most prevalent in Okinawa, followed by HCV and HBV. The prevalence of HBV was relatively higher in Hokkaido, Kyushu and in some western areas, and NASH was also more frequent (10%; fivefold higher than in other areas) in Japan.

Differences between males and females

Figure 3a shows differences in the etiology of LC between males and females. The ratio of alcohol was higher among males (19.2 vs. 4.3%; $P < 0.0001$, χ^2 test), whereas the ratios of PBC (0.6 vs. 5.3%), AIH (0.4 vs. 4.3%) and NASH (1.4 vs. 3.4%) were higher among females ($P < 0.0001$ for all). More female patients had LC of unknown etiology (2.3 vs. 4.0%, $P < 0.0001$). The numbers of males and females in the group with other known etiology were PSC, 44 and 22, Wilson's disease, 31 and 24 and hemochromatosis, 18 and 6, respectively.

Difference in etiology with or without HCC

The patients were categorized based on the presence of HCC, and then the etiology was analyzed (Fig. 3b). The

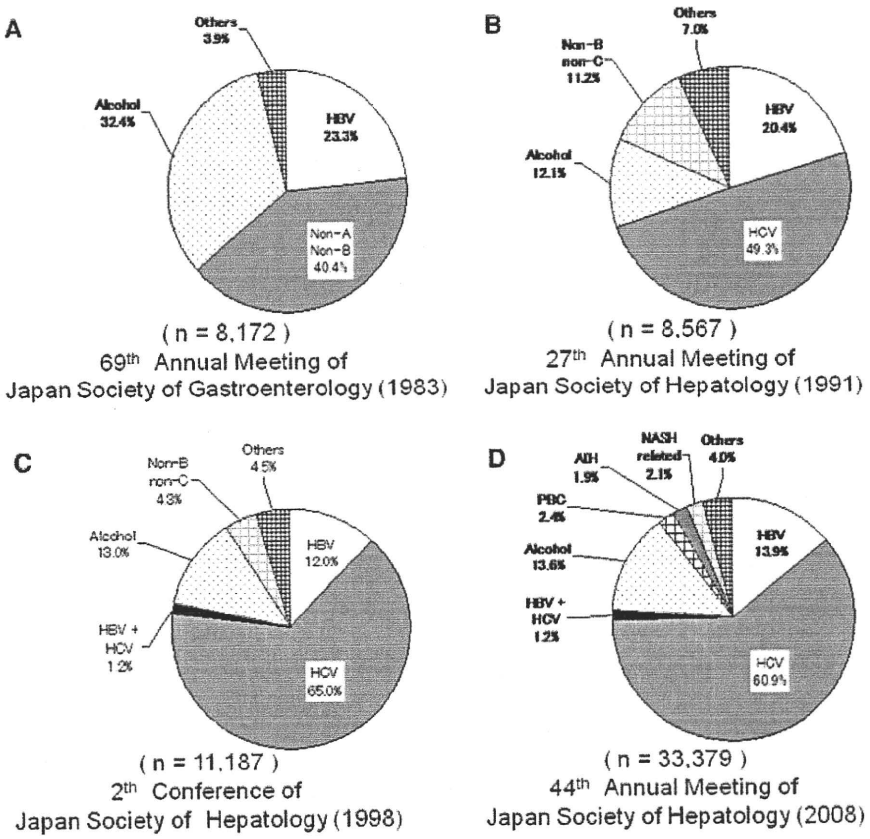

Fig. 1 Etiology of liver cirrhosis in Japan. Data presented at the 69th Annual Meeting of Japan Society of Gastroenterology in 1983 (edited by Dr. Sukeo Yamamoto) (**a**), 27th Annual Meeting of Japan Society of Hepatology in 1991 (edited by Dr. Yasuyuki Ohta) (**b**), 2nd Conference of Japan Society of Hepatology in 1998 (edited by Dr. Kennichi Kobayashi) (**c**), and 44th Annual Meeting of Japan Society of Hepatology (present study) (**d**)

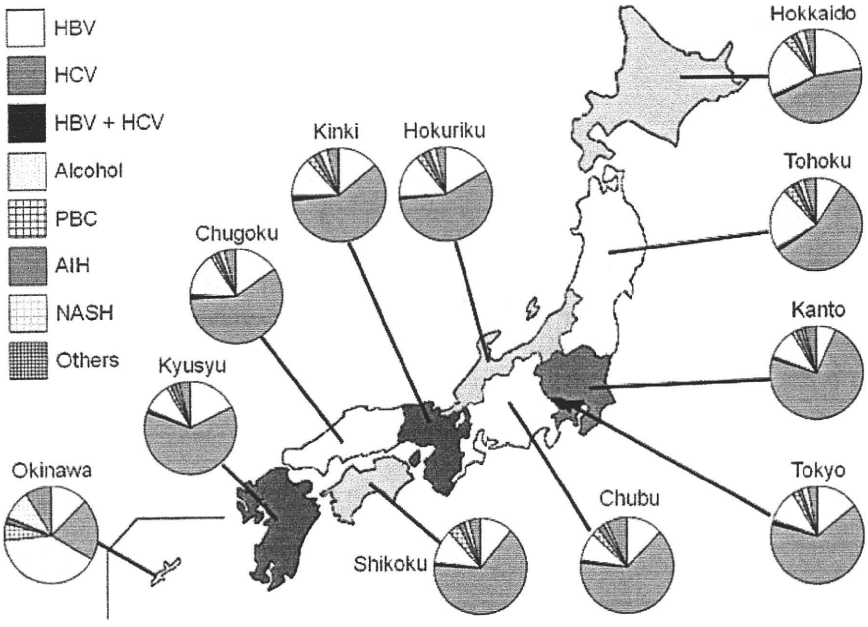

Fig. 2 Geographic distribution of etiology of liver cirrhosis in Japan

ratios among patients without HCC were HCV 49.4%, alcohol 20.5%, HBV 13.7%, PBC 4.0% and AIH 3.1%. On the other hand, the ratio of HCV was significantly higher (73.1%; $P < 0.0001$; χ^2 test), whereas those of alcohol, PBC, AIH were significantly lower (6.3, 0.6, 0.6%, $P < 0.0001$, respectively), and the findings were similar for HBV (14.1%). Among the metabolic diseases, HCC was complicated with Wilson's disease, hemochromatosis and

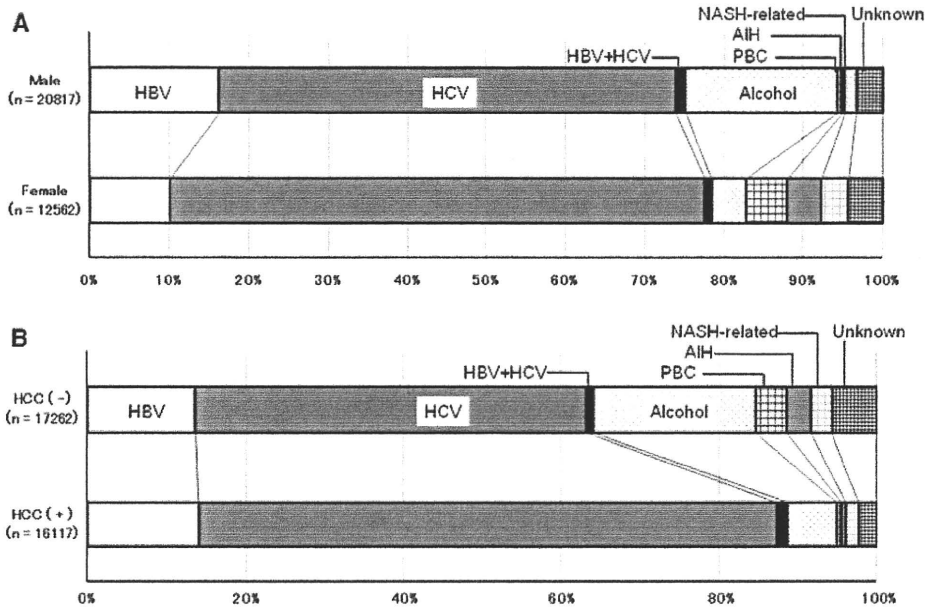

Fig. 3 Etiology of liver cirrhosis classified by gender and hepatocellular carcinoma. Data groups are separated based on gender (**a**) and hepatocellular carcinoma (**b**)

Table 3 Clinical features of NASH-related liver cirrhosis

	Total	Male (M)	Female (F)	*P* value (M vs. F)
Patients (%)	647	261 (40.3)	386 (59.7)	
Age (years)	66.6 ± 10.9	64.2 ± 12.2	68.2 ± 9.5	<0.001*
BMI (kg/m^2)	27.6 ± 4.5	26.9 ± 4.1	28.0 ± 4.8	<0.005*
Total cholesterol (mg/dl)	168.7 ± 49.1	170.1 ± 49.0	167.7 ± 49.2	NS
Triglyceride (mg/dl)	114.6 ± 114.6	124.5 ± 93.7	107.9 ± 68.0	<0.05*
Fasting plasma glucose (mg/dl)	138.6 ± 56.8	140.6 ± 58.5	137.2 ± 55.6	NS
Fasting insulin (μU/ml)	22.5 ± 25.2	20.1 ± 14.8	24.1 ± 30.3	NS
HOMA-IR	7.74 ± 9.24	7.51 ± 9.05	7.90 ± 9.41	NS
Hypertension (%)	316 (50.2)	110 (43.1)	206 (54.9)	<0.001*
Diabetes Mellitus (%)	424 (66.6)	175 (67.8)	249 (65.7)	NS
Hepatocellular carcinoma (%)	199 (31.5)	109 (42.2)	90 (24.1)	<0.05*

NS not significant

* *P* value determined by Student's *t* test

glycogen storage disease in 2 of 55, 4 of 24 and 2 of 5 patients, respectively.

NASH-related cirrhosis

Nonalcoholic steatohepatitis was associated with 2.1% of all LC; that is, in 2.7 and 1.6% of the groups without and with HCC complications, respectively. Table 3 shows the clinical background including laboratory data, complications and features of NASH-related LC in 647 patients. Mean age and body mass index (BMI) were 66.6 ± 10.9 and 27.6 ± 4.5, respectively. The women were older and had a higher BMI ($P < 0.001$ and <0.005, respectively) than the men. Hypertension and diabetes mellitus were complications in 50.2 and 66.6%, respectively, of those with NASH-related LC. HCC was frequently complicated with NASH-related LC (31.5%), especially among males (males vs. females: 42.2 vs. 24.1%, $P < 0.005$). Moreover, 10% of NASH-related LC was complicated with HCC during our 10-year study period. However, precise data about the study period of each followed-up patient was unavailable, so the accurate occurrence rate of HCC among patients with NASH could not be determined from this study. The prevalence of hypertension was higher in women, whereas that of HCC was higher among men. Anti-nuclear antibody (ANA) was found in 36.7% of all patients (males vs. females: 31.5 vs. 37.2%). One-third of patients with NASH were also positive for ANA, and the

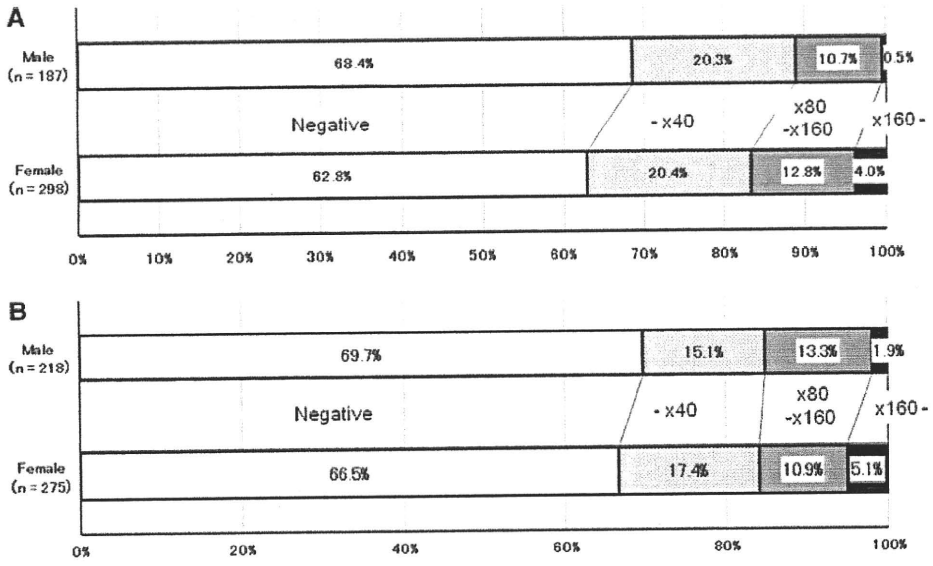

Fig. 4 Prevalence of anti-nucleic antibody (ANA) in liver cirrhosis that is NASH-related and of unknown etiology. Data show prevalence of ANA in LC related to NASH (**a**), and in LC of unknown etiology classified according to gender (**b**)

Table 4 Clinical features of liver cirrhosis of unknown etiology

	Total	Male (M)	Female (F)	*P* value (M vs. F)
Case (%)	801	385 (48.1)	416 (51.9)	
Age (years)	68.6 ± 11.1	66.8 ± 11.4	70.3 ± 10.5	<0.001*
BMI (kg/m^2)	23.9 ± 4.3	23.6 ± 3.8	24.2 ± 4.7	<0.001*
Total cholesterol (mg/dl)	152.4 ± 46.8	155.3 ± 51.1	149.7 ± 42.5	NS
Triglyceride (mg/dl)	88.3 ± 53.0	94.7 ± 58.6	82.4 ± 46.6	<0.01*
Fasting plasma glucose (mg/dl)	118.1 ± 46.6	118.5 ± 42.2	117.8 ± 50.3	NS
Fasting insulin (μU/ml)	14.0 ± 12.2	14.4 ± 14.4	13.6 ± 10.2	NS
HOMA-IR	4.0 ± 3.8	3.9 ± 2.8	4.2 ± 4.5	NS
Hypertension (%)	230 (30.7)	97 (27.6)	133 (33.5)	NS
Diabetes mellitus (%)	229 (30.3)	120 (33.8)	109 (27.3)	<0.001*
Hepatocellular carcinoma (%)	248 (32.6)	157 (43.0)	91 (23.0)	<0.001*

NS not significant

* *P* value determined by Student's *t* test

prevalence of ANA positivity was higher among females than males ($P < 0.005$; Fig. 4a).

Table 2 shows that we diagnosed NASH-related LC in one group that had been histologically diagnosed with NASH (39.4%; 255/647), and in another with clinically supposed NASH (60.6%; 392/647) without a histological examination. The frequency of HCC did not differ between histologically proven and supposed NASH (28.2 vs. 33.6%). Moreover, the positive rates of HBc antibodies did not differ between NASH-related LC with and without HCC (22.2 vs. 23.0%). We could not identify any other significant differences in the backgrounds of the patients between these groups. The positive ratio for ANA also did not differ between histologically diagnosed and supposed NASH (33.0 vs. 36.8%, respectively).

Cirrhosis of unknown etiology

We found LC of unknown etiology in 3.0% of the patients (3.8 and 1.8% with and without HCC complications, respectively). Table 4 shows the clinical data of 801 patients (mean age 68.6 ± 11.1 years). Age, BMI, triglyceride levels and HCC occurrence were significantly higher among females than males, findings similar to those of NASH-related LC (Table 3). Complication with diabetes mellitus was more prevalent among males than females among the patients with LC of unknown etiology. On the other hand, hypertension was more evident in females than in males among the patients with NASH-related LC. ANA was found in 33.9% of all patients (males vs. females: 30.3 vs. 33.5%; Fig. 4b). The positivity rate in females was

higher than that in males ($P < 0.005$), but that of ANA did not differ between total LC of unknown etiology and NASH-related LC (33.9 vs. 36.7%, respectively).

Discussion

The present study confirmed that HCV infection is the most prevalent cause of LC in Japan, accounting for about 60% of all LC. The induction of LC by HBV and alcohol was similarly prevalent, and these comprised the second and third most prevalent etiological factors. Causes related to NASH accounted for only 2.1% of LC in Japan. Among other types of metabolic cirrhosis, Wilson's disease was the leading cause, followed by hemochromatosis. A comparison with previous Japanese data showed that HCV remains the major etiology of liver cirrhosis in Japan, while the ratio of HBV has decreased over the past 17 years (Fig. 1b). Patients in Japan become infected with HCV at peak ages that are about 10–20 years older than those in the USA and European countries [11]. The present etiological features of HCV-induced LC in Japan are thus likely to be reflected in the USA and in European countries 10–20 years later.

The distribution of the etiology of liver cirrhosis in each area was similar in all geographic areas of Japan except Okinawa (Fig. 2), which was under American occupation for 27 years after World War II. Compared with other parts of Japan, Okinawa has more American cultural influences including food (such as fast-foods that have higher fat content and more calories). By the year 2000 (60 years after World War II), the mean lifespan in Okinawa had decreased from being the longest in Japan, while the prevalence of obesity had increased to being the highest in Japan [12, 13]. Such influences will be related to the increased ratio of NASH compared with other areas of Japan. Moreover, the prevalence of alcohol-related cirrhosis is higher and the ratio of HCV is lower in Okinawa than in other areas of Japan. These reasons will be clarified in future studies.

We analyzed the data based on gender and HCC (Fig. 3). The results indicated that alcohol-induced LC is more predominant among males, whereas HCV, autoimmune liver diseases (AIH or PBC) and NASH are more predominant among females. AIH occurs more frequently among females, and males consume more alcohol than females in Japan. Annual health screening has revealed that more males are HBs-antigen positive [14], whereas the frequency of HCV-antibody positivity is similar in both males and females [15]. More females than males had LC of unknown etiology. We suspect that this group included some patients with autoimmune or NASH-related cirrhosis that was not classified by the present criteria.

The ratios of etiologies among patients with HCC in the present study were comparable with those of other national surveys of HCC in Japan [16]. Additionally, our analyses clarified differences in etiological ratios between LC with and without HCC (Fig. 3). The ratio of HCV was higher among LC patients with HCC (67.2 vs. 57.5%, $P < 0.0001$), indicating that HCV itself has the potential to evoke hepatocarcinogenesis in patients with LC. On the other hand, HBV, alcohol, AIH and NASH would have less potential to evoke HCC than HCV. Although a prospective study is required to confirm this notion, these data are nevertheless sufficient to suggest that HCV infection contributes to hepatocarcinogenesis. Notably, many patients with HCC also had LC caused by alcohol, PBC, AIH and that related to NASH. Therefore, cirrhotic patients with not only viral hepatitis but also with these non-viral etiologies should be screened for HCC.

Recently, NASH has become recognized as an important cause of LC. Diagnostic criteria for nonalcoholic fatty liver disease (NAFLD) or NASH have been discussed elsewhere [17, 18]. Although the gold standard for a diagnosis of NASH is a liver biopsy, a risk of sampling error persists [17]. Furthermore, to obtain liver biopsies from patients with advanced cirrhosis is hazardous. Therefore, the actual prevalence of NASH-related LC has been difficult to define. Cryptogenic cirrhosis is thought to include NASH-related LC, and metabolic syndrome (MetS) is often a complication of NASH [18]. However, the importance of NASH in the etiology of liver cirrhosis remains ambiguous.

We considered that clinical etiologic criteria without a liver biopsy are needed to determine the accurate ratios of NASH-related cirrhosis due to the above reasons. The etiological criteria for clinically supposed NASH-related cirrhosis satisfied all of the factors listed in Table 2. We included obesity, diabetes mellitus (DM) and MetS among these criteria. The backgrounds of the patients diagnosed histologically and non-histologically with NASH-related LC did not differ. Under this classification, 0.9 and 1.2% of the 2.1% of patients with NASH-related LC were diagnosed histologically and non-histologically, respectively. Bell et al. reported that NAFLD accounted for 14.7% of LC in USA [4]. Thus, the frequency of NASH (NAFLD)-related LC is lower in Japan than in the USA, as is the frequency of MetS [19, 20]. The data show that the present frequency of NASH-related LC in Japan is quite low. However, the frequency of NASH-related LC will increase in Japan due to alterations in lifestyles (such as increased food consumption, type of food, stress and sedentary lifestyles), whereas that of HCV or HBV-related LC will decrease [21], as shown in Okinawa.

The frequency of HCC combined with NASH-related LC was high, especially among males (Table 3). The total

frequency of HCC in NASH-related LC herein was higher than in previous reports [22]. One reason for this is that our criteria for NASH-related LC included patients with higher-risk HCC compared with other studies. However, the frequencies of HCC in histologically defined and non-histologically supposed NASH did not differ. Another explanation is that occult HBV could be related to hepatocarcinogenesis in NASH-related HCC. However, the positivity rates of HBc antibody did not differ between NASH-related LC with and without HCC. Thus, the above factors probably did not influence our results. The reported incidence of HCC is higher in males with type 2 DM than in females [23, 24]. This evidence might be related to our findings, but further studies are required to reach a conclusion.

According to our criteria, cryptogenic LC (or LC of unknown etiology) of patients who do not consume alcohol but who were obese or complicated with DM or MetS were classified as having NASH-related LC. On the other hand, some patients with NASH-related cirrhosis without obesity, DM and MetS might have been included in the group with LC of unknown etiology. This group accounted for 3% of the studied patients, which was lower than that previously reported [1, 3, 4]. This group included LC due to viruses other than HBV and HCV, undiagnosed congenital diseases, undiagnosed AIH and patients with NASH who did not fulfill the study criteria. Patients who had been HBV carriers but who had become negative for HBsAg, or patients with occult HBV might have also been included [25]. However, the backgrounds of the male and female patients with NASH-related LC and LC of unknown etiology were quite similar (Tables 3, 4), as were the positivity and distribution of the ANA titers in both groups (Fig. 4). Further studies should clarify the real cause of LC with unknown etiology. Nevertheless, the present results suggest that some patients with NASH-related LC were included in the group with unknown etiology, rather than patients with undiagnosed AIH who are positive for ANA. If so, the estimated frequency of NASH-related LC will be 5–6% of all LC.

Our nationwide survey determined the etiology of liver cirrhosis in Japan. Infection with HCV remains a major cause of LC, and the ratio has persisted at around 60% for 10 years. Liver cirrhosis associated with HCV accounted for significantly more patients with LC with HCC than without, suggesting that HCV has carcinogenic potential. NASH-related LC accounted for 2.1% of the total LC in Japan and this might increase in the future. The present epidemic status in Japan might reflect the status of LC in the USA and European countries 10–20 years later.

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Appendix

The Japan Etiology of Liver Cirrhosis Study Group consists of the following members: Takashi Goto (Akita University), Mamiko Takeuchi (Anjo Kosei Hospital), Shigeki Miyoshi (Asahikawa Medical College), Yutaka Yonemitsu (Chiba University), Ikuta Tanaka (Date Red Cross Hospital), Toshimitsu Murohisa (Dokkyo Medical University School), Yoshio Tokumoto (Ehime University Graduate School of Medicine), Yoshinori Horie (Eiju Sogo Hospital), Atsushi Takahashi (Fukushima Medical University School of Medicine), Makoto Shiraki (Gifu University Graduate School of Medicine), Hiroko Yamada (Gunma University Graduate School of Medicine), Ryoichi Okamoto (Hiroshima City Hospital), Takahiro Asakami (Hiroshima University), Shuhei Hige (Hokkaido University Hospital), Yoshiaki Inui (Hyogo Prefectural Nishinomiya Hospital), Kazuto Fukuda (Ikeda Municipal Hospital), Yuko Nagaoki (International Medical Center of Japan), Hidekatsu Kuroda (Iwate Medical University), Takuya Nagano (Kagawa Prefectural Central Hospital), Akihiro Deguchi (Kagawa University School of Medicine), Masayoshi Yamada (Kanazawa Medical University), Akito Sakai (Kanazawa University Graduate School of Medical Science), Nobuyuki Toshikuni (Kawasaki Hospital, Kawasaki Medical School), Keisuke Ojiro (Keio University School of Medicine), Chitomi Hasebe (Keiyukai Yoshida Hospital), Yoko Kudo (Kumamoto University of Medicine), Kazuhisa Nakamura (Kyorin University School of Medicine), Kanji Yamaguchi (Kyoto Prefectural University of Medicine), Eiji Takeshita (Matsuyama Red Cross Hospital), Satoshi Nakayama (Mishuku Hospital), Yuka Takahashi (Musashino Red-Cross Hospital), Shunsuke Nojiri (Nagoya City University Graduate School of Medical Sciences), Masao Fujimoto (Nara Medical University), Naota Taura (NHO Nagasaki Medical Center), Hiroshi Matsumura (Nihon University School of Medicine), Minoru Nomoto (Niigata University), Shinichi Fujioka (Okayama Saiseikai General Hospital), Bon Shoji (Okayama University Graduate School of Medicine), Hiroyasu Morikawa (Osaka City University School of Medicine), Ryoichi Ebara (Osaka Police Hospital), Mie Inao (Saitama Medical University), Ayana Endo (Sapporo City General Hospital), Hideyuki Nomura (Shin-Kokura Hospital), Satoru Jyoshita (Shinshu University School of Medicine), Yoshihiko Morisawa (Teikyo University School of Medicine), Takeshi Matsui (Teine Keijinkai Hospital), Masanori Ito (Tokyo Medical University Kasumigaura Hospital), Naoaki Hashimoto (Tokyo Teishin Hospital), Maki Tobari (Tokyo Women's Medical University), Miharu Hirakawa (Toranomon Hospital), Kenji Oyama (Tottori University), Shingo Arakaki (University of Ryukyus), Makoto Kadokura (University of Yamanashi), Masanori Matsuda

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REVIEW

Hepatic encephalopathy as a complication of liver cirrhosis: An Asian perspective

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Key words
Asian cohort, drug therapy, hepatic encephalopathy, incidence, liver cirrhosis, liver transplantation, pathophysiology, treatment, response rate, survival rate.

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Abstract

Hepatic encephalopathy is one of the most important clinical manifestations in decompensated liver cirrhosis. Accepted concepts regarding the pathophysiology of hepatic encephalopathy are that the endogenous neurotoxic substances, including ammonia: (i) escape from catabolism by the liver due both to the impaired function of the cirrhotic liver and also to the presence of portal systemic shunting; (ii) circulate at elevated concentrations in the systemic blood flow; (iii) reach the brain through the blood-brain barrier; and (iv) impair cerebral function leading to disturbances of consciousness. The majority of these toxic substances are produced in the intestine by the bacterial flora, and are absorbed into the portal venous flow. The epidemiology of liver cirrhosis depends particularly on its etiology, and shows a marked geographic difference worldwide between Western, and Asian countries. Hepatic encephalopathy developed at an annual rate of 8% in cirrhotics in Far Eastern studies. In Eastern and Far East countries, therapeutic options are similar to those in the western hemisphere, but pronounced application of dietary restriction, antimicrobial agents, disaccharides, shunt obliteration and branched chain amino acids is noted. In spite of improved therapeutic options for encephalopathy, the long-term survival is still low. Thus, hepatic encephalopathy remains a serious complication of liver cirrhosis. Establishment of truly effective prevention modalities and broader application of liver transplantation will help rescue patients suffering from this complication of liver cirrhosis in the near future.

Introduction

Hepatic encephalopathy is one of the most important clinical manifestations in decompensated liver cirrhosis and, on this entity, much description has already been made.[1] However, the majority of this literature comes from Western countries, where the ethnicities as well as etiologies of liver cirrhosis differ largely from Eastern and Far East countries. Particularly focusing on this point of view, we attempt in this review article to elucidate an Asian perspective on clinical characteristics of hepatic encephalopathy as a complication of liver cirrhosis.

Pathophysiology

Mechanisms of the development of hepatic encephalopathy should be understood precisely in order to establish recommendations for the diagnosis and treatment of this clinical manifestation in liver cirrhosis. Although complete agreement has not yet been reached, the currently accepted concepts to explain the pathophysiology of cirrhotic encephalopathy are that: (i) the endogenous neurotoxic substances, including ammonia, escape from catabolism by the liver, due both to the impaired function of the cirrhotic liver and also to the presence of portal systemic shunt; (ii) these then circulate at elevated concentrations in the systemic blood flow; (iii) reach the brain through the blood-brain barrier; and (iv) impair cerebral function leading to altered higher functions and consciousness (Fig. 1). The majority of these toxic substances are produced in the intestine by the bacterial flora, and are absorbed into the portal venous flow.[2,3] Candidate substances include ammonia,[2,3] glutamine,[4] methionine and related monoamines, serotonin,[5] benzodiazepines,[6] and gamma-amino-butyric acid (GABA).[7] Regarding the microorganisms in the intestinal flora, anerobes seem to be particularly responsible for synthesis of such nitrogenous compounds from food origins.[8,9]

Diagnosis

In cases that are already known to have liver cirrhosis, the diagnosis of hepatic encephalopathy is relatively straight forward since the neurologic and psychiatric symptoms appear with other signs of liver failure, such as ascites and jaundice (Table 1). Otherwise, differential diagnosis includes any disease that can lead to disturbance of consciousness, including cerebrovascular disorders, central nervous infections, cardiovascular diseases and syncope,