Statistical analysis

Statistical testing was performed using SPSS version 15.0J (SPSS, Tokyo, Japan). Results were presented as means ± SD. Continuous variables were compared using one-way factorial analysis of variance (ANOVA) and multiple comparisons with Tukey and Dunnett's T3 methods. Categorical data were compared using the χ^2 test, and further, we carried out an analysis of residuals in cross tabulation.

Results

Demographic and clinical features and outcome of patients with acute liver failure

As shown in Table 1, of the total study population, 40.2% had underlying diseases such as metabolic syndrome, and most of such patients were on daily medications. The etiology of fulminant hepatitis was viral infection in 69.3, 31.2, and 17.1% of the patients in group-A, group-B, and group-C, respectively. In most cases, the causative virus was HBV; transient infection was predominant in group-A, whereas asymptomatic carriers showing acute exacerbation of hepatitis predominated in group-B. The survival rates of the 811 patients who received medical treatment alone (without LT) were 53.4% in group-A, 24.5% in group-B, and 12.1% in group-C (Table 2).

Clustering analysis of the patients with acute liver failure

The results of analysis by the SOM technique revealed that the acute liver failure patients could be classified into three clusters, consisting of 411, 320, and 291 patients, respectively: cluster-1 (40.2%), cluster-2 (31.3%), and cluster-3 (28.5%). The demographic and clinical features of the patients in each cluster are shown in Tables 4, 5, 6, and 7 and Fig. 1.

As shown in Table 4, the interval between the onset of the hepatitis symptoms and the development of hepatic encephalopathy differed among the three clusters; the percentages of patients belonging to group-A, group-B, and group-C were 56.7, 39.2, and 4.1%, respectively, in cluster-1, and 58.8, 34.0, and 7.2%, respectively, in cluster-3. However, in cluster-2, the percentage of patients belonging to group-A was smaller, and those of patients belonging to group-B and group-C were greater (21.3, 65.0, and 13.8%, respectively) than in either cluster-1 or cluster-3.

Also, the demographic features of the patients differed among the three clusters (Table 5). There were a greater number of females in both cluster-1 and cluster-2 than in cluster-3, while the number of males was higher than that of females in cluster-3. The age (years: mean ± SD) of the patients was significantly higher in cluster-2 (54.9 ± 15.6) than in cluster-1 (41.0 ± 16.2) or cluster-3 (51.5 ± 14.2), and the age in cluster-3 was also significantly higher than that in cluster-1. The age distribution of the patients in each cluster is shown in Fig. 1. The percentage of HBV carriers was especially high in patients in cluster-3 (23.0%) compared with those in cluster-1 (7.9%) and cluster-2 (12.7%). In contrast, the underlying diseases preceding acute liver failure, such as metabolic syndrome, malignancies, and psychiatric disorders, were found more frequently in patients in cluster-2 (54.0%) and cluster-3 (49.3%) than in the patients in cluster-1 (23.3%). Such a tendency was also noted for the percentages of patients receiving previous medications (34.4, 60.1, and 53.7%, respectively, in cluster-1, cluster-2, and cluster-3).

Table 5 shows the relation between the etiology of the liver disease and the classification depending on the SOM analysis in the patients with acute liver failure. Viral infection was the most prevalent etiology in the patients in cluster-1 (53.0%) and cluster-3 (63.6%), but the causative virus differed between these clusters. Although the percentage of patients with transient HBV infection was similar in cluster-1 and cluster-3 (29.4 and 31.6%, respectively), the percentage of HBV carriers with hepatitis exacerbation was higher in cluster-3 (20.6%) as compared

Table 4 Intervals between the onset of hepatitis symptoms and grade II or more severe hepatic encephalopathy in acute liver failure patients and their clusters according to the classification by the self-organizing map

Groups[a]	% (Number of patients)			
	Total (n = 1,022)	Cluster-1 (n = 411)	Cluster-2 (n = 320)	Cluster-3 (n = 291)
Group-A	46.2 (472)	56.7 (233)*	21.3 (68)	58.8 (171)*
Group-B	45.8 (468)	39.2 (161)*	65.0 (208)	34.0 (99)*
Group-C	8.0 (82)	4.1 (17)*,#	13.8 (44)	7.2 (21)*

* $p < 0.05$ versus cluster 2; # $p < 0.05$ versus cluster 3 by χ^2 test and analysis of residuals in cross tabulation

[a] The interval between the onset of the hepatitis symptoms and the development of grade II or more severe hepatic encephalopathy was 10 days or less (group-A), between 11 and 56 days (group-B), and more than 56 days (group C)

Table 5 Demographic features and etiology of acute liver failure patients and their clusters according to the classification by the self-organizing map

	Total (n = 1,022)	Cluster-1 (n = 411)	Cluster-2 (n = 320)	Cluster-3 (n = 291)
Male:female (:unknown)	498:523 (:1)	187:224	122:197 (:1)	189:102*,#
Age (years)	48.3 ± 16.7[a]	41.0 ± 16.2	54.9 ± 15.6†	51.5 ± 14.2†,‡
HBV carrier [% (n)]	13.4 (126/940)	7.9 (31/390)	12.7 (39/306)*	23.0 (56/244)*,#
Underlying diseases[b] [% (n)]	40.2 (404/1,005)	23.3 (95/408)	54.0 (169/313)*	49.3 (140/284)*
Previous medication [% (n)]	47.7 (466/977)	34.4 (139/404)	60.1 (182/303)*	53.7 (145/270)*,#
Etiology [% (n)]				
Viral infection	47.7 (487)	53.0 (218)	26.3 (84)*	63.6 (185)#
HAV	5.4 (55)	9.0 (37)	1.6 (5)*	4.5 (13)*,#
HBV	39.5 (404)	40.1 (165)	22.2 (71)*	57.7 (168)*,#
Transient infection	22.8 (233)	29.4 (121)	6.3 (20)*	31.6 (92)#
Carrier	13.1 (134)	7.5 (31)	13.4 (43)*	20.6 (60)*,#
Undetermined	3.6 (37)	3.2 (13)	2.5 (8)	5.5 (16)*,#
HCV	1.3 (13)	1.7 (7)	1.9 (6)	0.0 (0)*,#
HEV	0.7 (7)	1.2 (5)	0.0 (0)	0.7 (2)
Other virus	0.8 (8)	1.2 (5)	0.3 (1)	0.7 (2)
Autoimmune hepatitis	7.8 (80)	5.4 (22)	15.3 (49)*	3.1 (9)#
Drug allergy-induced	11.0 (112)	9.2 (38)	15.9 (51)*	7.9 (23)*,#
Indeterminate	31.2 (319)	30.2 (124)	40.9 (131)*	22.0 (64)*,#
Insufficient examinations[c]	2.3 (24)	1.9 (8)	1.9 (6)	3.4 (10)

HBV hepatitis B virus, *HAV* hepatitis A virus, *HCV* hepatitis C virus, *HEV* hepatitis E virus

† $p < 0.05$ versus cluster 1; ‡$p < 0.05$ versus cluster 2 by one-way ANOVA and multiple comparisons

* $p < 0.05$ versus cluster 1; #$p < 0.05$ versus cluster 2 by χ^2 test and analysis of residuals in cross tabulation

[a] Mean ± SD

[b] Diseases such as metabolic syndrome, malignancy, and psychiatric disorders

[c] The etiology was unknown because of insufficient examinations

with that in cluster-1 (7.5%). In contrast, the percentages of patients with drug-induced liver injury, autoimmune hepatitis, and those with indeterminate etiology was higher in cluster-2 (15.9, 15.3, and 40.9%, respectively) than in cluster-1 (9.2, 5.4, and 30.2%, respectively) or cluster-3 (7.9, 3.1, and 22.0%, respectively).

As shown in Table 6, the frequencies of complications, such as bacterial infection, gastrointestinal bleeding, renal and cardiac failure, DIC, and cerebral edema, differed among the three clusters. There were no complications in 56.9% of the patients in cluster-1, while the percentages of patients with no complications were as low as 11.9 and 1.4% in cluster-2 and cluster-3, respectively. The percentage of patients with 2 or more complications was 11.9% in cluster-1, which was markedly lower than the values in cluster-2 (54.4%) and cluster-3 (90.4%).

Consequently, the outcome of the patients differed markedly among the three clusters (Table 7). LT was performed in 34.3% of the patients in cluster-1, which was a significantly greater percentage than the corresponding percentages in cluster-2 (15.6%) and cluster-3 (6.9%), and the survival rates of these patients with LT were 90.1, 52.0, and 60.0% in cluster-1, cluster-2, and cluster-3, respectively. Also, the survival rate in the patients not treated by LT was significantly higher in cluster-1 (94.4%) than in cluster-2 (6.7%) or cluster-3 (12.9%). The survival rate among patients receiving medical treatment alone was still significantly higher in cluster-1 (62.0%) than in cluster-2 (5.6%) or cluster-3 (12.0%), even when it was expressed as the ratio of number of survivors to the total number of patients including those receiving liver transplantation.

Discussion

In this study, the validity of the classification of acute liver failure according to the interval between the onset of the hepatitis symptoms and the development of hepatic encephalopathy was evaluated. Previous classifications were established based on decision analyses with a linear mode, such as multivariate regression analysis. Such analysis, however, is not suitable for modeling complex multidimensional relationships, which may also affect the prognosis of acute liver failure patients in a complex

Table 6 Numbers of complications in acute liver failure patients during the whole course of the disease and their clusters according to the classification by the self-organizing map

Number of complications	% (Number of patients)			
	Total (n = 1,022)	Cluster-1 (n = 411)	Cluster-2 (n = 320)	Cluster-3 (n = 291)
0	27.0 (276)	56.9 (234)	11.9 (38)*	1.4 (4)*
1	25.4 (260)	31.1 (128)	33.8 (108)	8.2 (24)*,#
2	20.3 (207)	10.2 (42)	28.8 (92)*	25.1 (73)*
3	14.2 (145)	1.7 (7)	16.6 (53)*	29.2 (85)*,#
4	7.9 (81)	0.0 (0)	6.6 (21)*	20.6 (60)*,#
5	3.7 (38)	0.0 (0)	2.5 (8)*	10.3 (30)*,#
6	0.9 (9)	0.0 (0)	0.0 (0)	3.1 (9)*,#

* $p < 0.05$ versus cluster 1; # $p < 0.05$ versus cluster 2 by χ^2 test and analysis of residuals in cross tabulation

Table 7 Outcome of acute liver failure patients and their clusters according to the classification by the self-organizing map

	% (Number of patients)			
	Total (n = 1,022)	Cluster-1 (n = 411)	Cluster-2 (n = 320)	Cluster-3 (n = 291)
Survival rates in all patients	46.2 (473/1,022)	92.9 (382/411)	13.8* (44/320)	16.2* (47/291)
Treated without liver transplantation	79.4 (811)	65.7 (270)	84.4 (270)	93.1 (271)
Survival rates with medical treatment alone in all patients	30.1 (308/1,022)	62.0 (255/411)	5.6* (18/320)	12.0* (35/291)
Survival rates in patients receiving medical therapies alone	38.0 (308/881)	94.4 (255/270)	6.7* (18/270)	12.9* (35/271)
Treated by liver transplantation	20.6 (211)	34.3 (141)	15.6 (50)	6.9 (20)
Survival rates	78.1 (165/211)	90.1 (127/141)	52.0* (26/50)	60.0* (12/20)

* $p < 0.05$ versus cluster 1 by χ^2 test and analysis of residuals in cross tabulation

manner. Thus, we evaluated the validity of the classification using artificial neural networks, one of the decision analyses with a non-linear mode.

The SOM is a neural network methodology that has been used for the categorization and interpretation of multidimensional data sets with a large scale [8]. The categorization can be achieved through transformation of an n-dimensional input vector into an r-dimensional separated map, in which r is smaller than n and is usually 2. Thus, the input vectors are preserved on the same area of the map, and these signal processing units are called "neurons". Each neuron shows an association through an n-dimensional reference vector that determines the linkage between the maps of the input and output vectors. The input vector is transformed onto a particular neuron through the calculation in which the n-dimensional distance between the input and reference vectors of the neuron is the minimal distance. Based on such calculations, the reference vectors of the neurons are updated repeatedly, and finally the best-matching neurons are established. As a result, the SOM can accomplish clustering of the input data sets without the experience of specialists. Such a process is called unsupervised learning.

In the present study, the results of the clustering analysis using the SOM revealed that the patients with acute liver failure could be classified into three clusters different from the disease groups, depending on the interval between the onset of the hepatitis symptoms and the development of hepatic encephalopathy as nominal variables. Also, similar results were obtained in analysis when such intervals were assessed as continuous variables (data not shown). As shown in Table 4, 404 of the 472 patients (85.6%) in group-A belonged to either cluster-1 or cluster-3. Also, while 208 of the 468 patients (44.4%) in group B and 44 of the 82 patients (53.7%) in group-C were classified into cluster-2, a distinct accumulation of the patients in these three clusters, as was the case in group-A, was not found in the other two groups. Moreover, it should be noted that the demographic and clinical features and the outcome differed between the patients in cluster-1 and those in cluster-3 (Tables 5, 6, and 7; Fig. 1), despite the percentages of patients belonging to groups A, B, and C being almost identical in these two clusters (Table 4). These observations strongly suggest that patients with acute liver failure in Japan may be classified into disease types different from those that are exclusively dependent on the interval between the onset of the hepatitis symptoms and the development of hepatic encephalopathy.

The novel classification through the SOM analysis may be clinically important, since the outcome of the patients

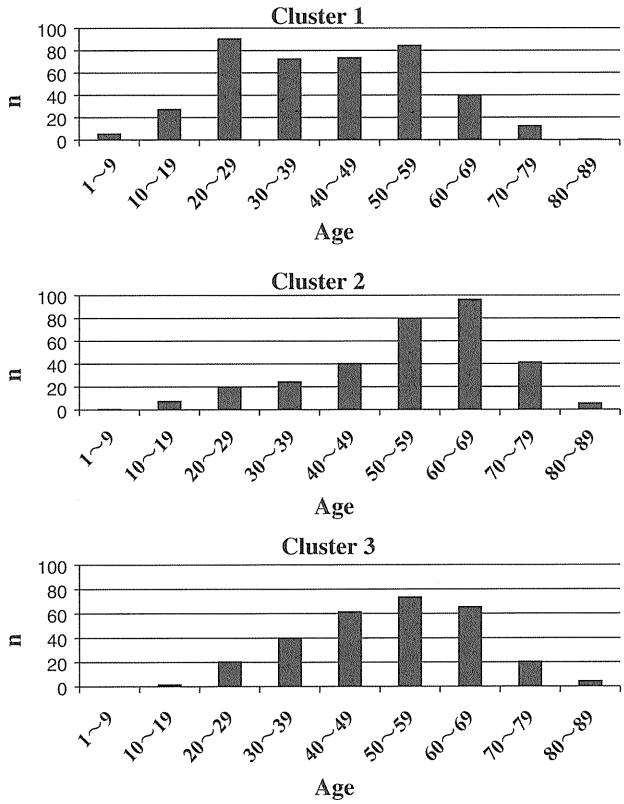

Fig. 1 Distribution of the ages (years) of acute liver failure patients classified according to the clustering analysis based on the self-organizing map

differed more obviously among the clusters as compared with the differences between the disease types determined based only on the interval from the onset of the hepatitis symptoms and the development of hepatic encephalopathy (Table 1). A total of 141 (66.8%) of the 211 patients treated by LT were classified into cluster-1, and the survival rate of these patients was 90.1%. Also, the survival rate of those treated conservatively without LT was extremely high (94.4%) in this cluster. In contrast, the percentage of the patients treated by LT was extremely low in cluster-2 and cluster-3, and 78.8% (252/320) and 81.1% (236/291) of the patients, respectively, who were treated conservatively without LT died. The factors that seemed to be responsible for the differences among these clusters were the sex and age of the patients, the presence of the underlying diseases and history of previous medications, the etiology of the liver diseases, and the number of complications developing during acute liver failure, as well as the interval between the onset of the hepatitis symptoms and the development of hepatic encephalopathy. The patients with such factors, among which complex multi-dimensional relationships may exist, could be classified into the clusters reflecting their outcome only through SOM analysis, a form of artificial neural network.

Our classification is also useful for speculating on the possible cause of acute liver failure in the patients with indeterminate etiology. Of the 319 patients with indeterminate etiology, 131 (41%) were classified into cluster-2, in which 61 and 46% of the patients in whom the acute liver failure was due to autoimmune hepatitis and drug-induced liver injury, respectively, were also classified. The total percentage of patients with indeterminate etiology and those whose acute liver failure was due to autoimmune hepatitis and drug-induced liver injury was 72% in this cluster. In contrast, 124 (39%) of the patients with indeterminate etiology were classified into cluster-1 and 64 (20%) into cluster-3. Viral infection was the most prevalent etiology in both clusters (53 and 64%, respectively, in cluster-1 and cluster-3), but the causative virus differed between these clusters; transient infections of HAV and HBV were dominant in cluster-1, while HBV carriers showing acute hepatitis exacerbation prevailed in cluster-3. Considering the characteristics of the patients with indeterminate etiology in each cluster, possible etiologies in these patients were transient unknown virus infection in cluster-1, autoimmune hepatitis or drug-induced liver injury in cluster-2, and HBV occult infection in cluster-3. These possibilities should be further investigated.

Although our classification may be useful to predict the outcome of patients with acute liver failure and the possible causes of the condition in those with indeterminate etiology, there still exist problems that need to be resolved preceding the application of the system for the benefit of hepatologists in Japan. First, the patients can be classified into the three clusters only through the SOM technique using the IBM Intelligent Miner software. Physicians and/or transplant surgeons are required to input the data sets on a total of 104 items collected from the patients using personal computers, and the clusters that the patients are categorized into are shown on the websites through a blind decision process. Such complicated procedures might prevent our system from becoming prevalent for clinical use by hepatologists nationwide. Simple algorithms, using which any physicians and/or surgeons can predict the outcome of the patients based on the clusters that they belong to, with no reference to the websites, should be established using data-mining analysis methods, such as the decision tree [17]. Secondly, the purpose of our system is to categorize patients with acute liver failure depending on the demographic and clinical features of the patients as well as their prognosis, suggesting that such a system may not always be suitable for determination of the indications for LT. For example, regarding cluster-1, in which the survival rate of the patients was extremely high, one-third of the patients were rescued after being treated by LT, while two-thirds survived following conservative treatment without transplantation. Thus, a system to directly predict

the prognosis of the patients should be established based on the data sets exclusively derived from the patients treated conservatively without LT. The radial basis function model [17, 18] and/or the back propagation model [19], one form of artificial neural network, would seem to be suitable for such analysis with the data-mining procedures. Also, precise information on past medical history, especially regarding underlying diseases and previous medication (which are important factors that determine the character of each cluster), should be analyzed. These projects should be undertaken in the future.

In the present study, patients with acute liver failure diagnosed according to the definition established in Japan were analyzed through the SOM technique. Analyses using the SOM technique in patients with acute liver failure in the United States and Europe also merit consideration, since the outcome prognosis of the patients may be determined through complex multidimensional relationships including the etiology, as well as the intervals between the onset of hepatitis symptoms and the development of hepatic encephalopathy [4, 20, 21]. There seems to be a higher percentage of patients that can be rescued without LT in these countries than in Japan, possibly because of the difference in the definition criteria of acute liver failure, especially in relation to the differences in criteria for prothrombin time among the countries [1–4]. Such patients may be identified through data-mining analysis using the SOM technique. Thus, such an approach may contribute to the overcoming of problems of organ shortage in the field of LT, which also exist in Europe and the United States.

In conclusion, patients with acute liver failure in Japan were classified into three clusters independent of the disease types depending on the interval between the disease onset and the development of encephalopathy, using the SOM technique. This technique may be useful for establishing prognosis prediction models, since the outcome of the patients differed markedly among the clusters.

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Special Report

Diagnostic criteria of acute liver failure: A report by the Intractable Hepato-Biliary Diseases Study Group of Japan

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The diagnostic criteria of fulminant hepatitis in Japan are different from those of acute liver failure in Europe and the United States, both in regard to the histological features in the liver and the cutoff values of the prothrombin time. Thus, the Intractable Hepato-Biliary Disease Study Group established novel diagnostic criteria for "acute liver failure" in Japan based on the demographic and clinical features of the patients. Patients showing prothrombin time values of 40% or less of the standardized values or international normalized ratios of 1.5 or more caused by severe liver damage within 8 weeks of onset of the symptoms are diagnosed as having "acute liver failure", where the liver function prior to the current onset of liver damage is estimated to be normal. Acute liver failure is classified into "acute liver failure without hepatic coma" and "acute liver failure with hepatic coma," depending on the severity of the hepatic encephalopathy; the latter is further classified into two types, the "acute type" and the "subacute type", in which grade II or more severe hepatic coma develops within 10 days and between 11 and 56 days, respectively, after the onset of disease symptoms. Patients without histological findings of hepatitis, such as those with liver damage caused by drug toxicity, circulatory disturbance or metabolic disease, are also included in the disease entity of "acute liver failure", while acute-on-chronic liver injuries, such as liver injury caused by alcohol, are excluded. A nationwide survey of "acute liver failure" in Japan based on the novel criteria is proposed.

Key words: acute liver failure, diagnostic criteria, fulminant hepatitis, hepatic encephalopathy, late onset hepatic failure

INTRODUCTION

DIFFERENCES EXIST IN the demographic and clinical features of patients with acute liver failure between Japan and Europe and/or the United States. Hepatitis viral infection is the most important and frequent cause of acute liver failure in Japan,[1] while acetaminophen-induced toxic liver injury prevails as the major cause of acute liver failure in Europe and the United States.[2] Thus, acute liver failure has been typically represented by fulminant hepatitis in Japan, and the diagnostic criteria for "fulminant hepatitis", which were different from those for "acute liver failure" in Europe and the United States, were established by the Inuyama Symposium in 1981.[3] According to the Inuyama Symposium criteria, patients with hepatitis were diagnosed as having fulminant hepatitis when they developed grade II or more severe hepatic encephalopathy within 8 weeks of the onset of hepatitis symptoms due to severe liver damage as represented by prothrombin time values of 40% or less as compared to the standardized values. Fulminant hepatitis was further classified into two disease types, acute and subacute types of fulminant hepatitis, on the basis of the

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Table 1 Diagnostic criteria for fulminant hepatitis in Japan established by the Intractable Liver Diseases Study Group of Japan, the Ministry of Health, Welfare and Labour (2003)

Fulminant hepatitis is defined as hepatitis with hepatic encephalopathy of grade II or more, develops in patients within 8 weeks of the onset of disease symptoms, and is associated with severe derangement of the liver function, including prothrombin time values of less than 40% of the standardized values. Fulminant hepatitis is classified into two subtypes: the acute type and the subacute type, according to whether the encephalopathy occurs within 10 days and later than 11 days, respectively, after the onset of the symptoms.

Note 1: Patients with chronic liver diseases are excluded from the disease entity of fulminant hepatitis, but asymptomatic hepatitis B virus (HBV) carriers developing acute exacerbation are included as cases of fulminant hepatitis.

Note 2: Acute liver failure with no histological evidence of liver inflammation, such as that caused by drug or chemical intoxication, circulatory disturbance, acute fatty liver of pregnancy or Reye's syndrome are excluded from fulminant hepatitis.

Note 3: The grading of hepatic encephalopathy is based on the criteria presented in the Inuyama Symposium in 1972.

Note 4: The etiology of fulminant hepatitis is based on the criteria established by the Intractable Liver Diseases Study Group of Japan in 2002.

Note 5: Patients with no or grade I encephalopathy, but showing prothrombin time values of less than 40% of the standardized values are diagnosed as having acute hepatitis, severe type. Patients in whom the encephalopathy develops between 8 and 24 weeks after the disease onset, with prothrombin time values of less than 40% of the standardized values are diagnosed as having late-onset hepatic failure (LOHF). Both are diseases related to fulminant hepatitis, but are regarded differently from fulminant hepatitis.

hepatic encephalopathy developing within 10 days and between 11 and 56 days, respectively, after the onset of the hepatitis symptoms. Fulminant hepatitis in Japan is defined as acute liver failure with histological evidence of hepatic inflammation, characterized by lymphocytic infiltration of the liver. Thus, the etiology of fulminant hepatitis includes viral infections, hepatitis B virus (HBV) carriers, autoimmune hepatitis, drug allergy-induced liver injuries, and hepatitis of indeterminate etiologies, but would exclude liver injuries caused by drug toxicity, circulatory disturbances, metabolic diseases, acute fatty liver of pregnancy, and postoperative liver damage, all of which are also included as etiological factors for disease entity of "acute liver failure" in Europe and the United States. Also, the extent of liver damage has been defined worldwide based on the degree of prolongation of the prothrombin time although the values are expressed as a percentage of the standardized values in Japan, but as the international normalized ratio (INR) in the United States.[2] Therefore, the diagnostic criteria for "fulminant hepatitis" in Japan need to be revised to correspond to those for "acute liver failure" in Europe and the United States.

The Intractable Liver Diseases Study Group of Japan, supported by the Ministry of Health, Labour and Welfare last revised the diagnostic criteria for "fulminant hepatitis" in 2002 (Table 1).[1,4] The definition and concept of fulminant hepatitis, however, were not modified, except that five items clarifying the inclusion and exclusion criteria for fulminant hepatitis were added to the footnotes. Thus, in 2006, the Intractable Hepato-Biliary Diseases Study Group of Japan (formerly the Intractable Liver Diseases Study Group of Japan) constituted a task force to establish novel diagnostic criteria for "acute liver failure", which includes the disease entity of "fulminant hepatitis". We report on the established criteria for "acute liver failure" available for Japanese patients.

METHODS

Expression of prothrombin time

A QUESTIONNAIRE WAS sent to active members of the Japan Society of Hepatology affiliated to 550 departments of gastroenterology and/or hepatology in 454 institutions in Japan, to determine what type of commercial kit they used for prothrombin time measurement in their clinical laboratories. Then, information regarding the International Sensitivity Index (ISI) values and INR values corresponding to 40% of the standardized values for each kit was collected from the respective industrial companies.

Evaluation of acute liver failure other than fulminant hepatitis in Japan

A questionnaire was sent to specialists of the Japanese Association of Acute Medicine in 533 institutions, including 218 emergency lifesaving centers and 235

emergency departments, to determine the demographic and clinical features and prognosis of acute liver failure patients hospitalized in their respective institutions between 2006 and 2008. Patients with prothrombin time values of 50% or less of the standardized values, or INRs of 1.5 or more, and those with grade II or more severe hepatic encephalopathy were enrolled; however, patients fulfilling the diagnostic criteria for fulminant hepatitis and late-onset hepatic failure (LOHF), a disease related to fulminant hepatitis,[5] were excluded from the database (Table 1). In contrast, patients with underlying chronic liver diseases were included in the evaluation. The patients were classified into five groups; namely, those without hepatic encephalopathy or with grade I hepatic encephalopathy (group 1), those showing grade II or more severe hepatic encephalopathy within 10 days, between 11 and 56 days, or later than 56 days after the onset of symptoms (group 2, group 3 and group 4, respectively), and those with underlying chronic liver diseases (group 5). The nationwide survey was conducted with the approval of the ethics committee of Kagoshima University Graduate School of Medical and Dental Sciences.

Development of diagnostic criteria for "acute liver failure" in Japan

The diagnostic criteria for "acute liver failure" were established based on the results of the following evaluations: (i) the nationwide surveys of fulminant hepatitis and LOHF conducted by the Intractable Liver Diseases Study Group of Japan between 1999 and 2004[1] and by the Intractable Hepato-Biliary Diseases Study Group of Japan between 2005 and 2009;[6–10] (ii) the survey of commercial kits used at institutions to which members of the Japan Society of Hepatology are affiliated; and (iii) the nationwide survey of acute liver failure patients who were not diagnosed as having fulminant hepatitis. The task force of the Intractable Liver Diseases Study Group of Japan prepared the preliminary criteria, and the criteria were completed through discussions among all members of the Study Group.

RESULTS

Commercial kits used for prothrombin time measurement in Japan

RESPONSES TO THE questionnaire were obtained from 359 institutions (79.1%). Sixteen types of commercial kits produced by six industrial companies were used, as shown in Table 2. The most frequently used kit was used in 39% of the institutions (138 institutions), and the kits ranked in the top six places, in terms of the frequency of use, accounted for 92% of the kits used at the institutions. The ISI values of these kits ranged from 0.81 to 2.05, thus, the INRs corre-

Table 2 Commercial kits used at institutions to which active members of the Japan Society of Hepatology are affiliated

Commercial kits	Industrial companies	Number of institutions	ISI	INR corresponding to 40% of the standardized values
A	Q	138	0.95–1.27	1.7
B	Q	50	1.21–1.80	1.9
C	Q	11	0.99–1.10	1.6
D	Q	47	1.44–2.05	1.9
E	Q	24	1.16–1.41	1.9
F	R	35	1.22–1.24	1.98
G	R	3	1.22	ND
H	R	2	1.00–1.02	1.86
I	S	27	0.81–1.00	1.7–1.9
J	S	1	1.8	1.8
K	S	1	1.06	2.1
L	T	3	1.18–1.21	1.7
M	T	1	1.65	2.0
N	T	2	1.07–1.10	1.9
O	U	4	1.73	2.12
P	V	1	1.09	ND

ND, not determined.

sponding to 40% of the standardized values differed markedly among the kits (range, 1.6 and 2.12). When the INRs for the kits ranked in the top six positions were evaluated, the mean INR was found to be 1.86 (range, 1.6 to 1.98).

Acute liver failure patients excluded from the disease entity of fulminant hepatitis in Japan

A total of 217 patients were enrolled from 58 institutions (12.8%), and they were classified as shown in Table 3. Hepatic encephalopathy was absent or grade 1 in 79 patients (group 1: 36.4%). In contrast, grade II or more severe hepatic encephalopathy was present in 94 patients (43.3%), and of these, 58, 34 and two patients, respectively, were classified into group 2 (26.7%), group 3 (15.7%) and group 4 (0.9%). The remaining 44 patients were diagnosed as having acute-on-chronic liver injury and were classified into group 5 (20.3%).

The etiologies of liver damage were viral infection, autoimmune hepatitis, drug allergy-induced liver injury, and indeterminate in 121 patients (55.8%). In the remaining 96 patients (44.2%), the etiologies consisted of those in the exclusion lists for fulminant hepatitis and LOHF. Among these, alcoholic liver injury was the most frequent etiology, noted in 43 patients (19.8%). Circulatory disturbance, malignant cell infiltration, drug toxicity-induced liver injury, postoperative liver injury and metabolic disease were noted as the etiologies in 18 (8.3%), eight (3.7%), eight (3.7%), two (0.9%) and one patient (0.5%), respectively. Most of these patients were classified into either group 1 or group 5.

The prognosis was excellent, especially for the group 1 patients, who showed a survival rate of 78% with conventional medical care. The survival rates, however, were lower for the patients belonging to the other groups, being 35%, 12%, 0% and 21%, respectively, for group 2, group 3, group 4 and group 5. A total of 110 patients died despite conventional medical care, and the causes of death were complications, such as bacterial infection, in 44 patients (40%). Especially, in patients with acute liver failure caused by alcoholic liver injury, multiple organ failure developed frequently, serving as the cause of death. Liver transplantation was performed in 10%, 12% and 50% of the patients in group 2, group 3 and group 4, respectively.

Diagnostic criteria for "acute liver failure" in Japan

The diagnostic criteria for "acute liver failure" in Japan are shown in Table 4. Patients showing prothrombin time values of 40% or less of the standardized values or INRs of 1.5 or more due to severe liver damage within 8 weeks of onset of the symptoms are diagnosed as having "acute liver failure", where the liver function prior to the current onset of liver damage is estimated to be normal. Patients without histological findings of hepatitis, such as those with liver injuries caused by drug toxicity, circulatory disturbance or metabolic disease,

Table 3 Disease groups and causative etiology of acute liver failure in patients not diagnosed as having fulminant hepatitis or late-onset hepatic failure

Groups†	Group-1	Group-2	Group-3	Group 4	Group-5	Total
Number of patients	79	58	34	2	44	217
Etiology‡	Percentage of patients in each type					
Viral	32.9	32.8	32.4	0	25.0	30.9
Drug allergy	5.1	13.8	17.6	50.0	2.3	9.2
Autoimmune	0	8.6	11.8	0	0	4.1
Indeterminate	11.4	8.6	17.6	50.0	4.5	10.6
Unclassified	0	3.4	0	0	0	0.9
Drugs toxicity	5.1	5.2	0	0	2.3	3.7
Alcoholic	17.7	12.1	8.8	0	43.2	19.8
Circulatory disturbance	15.2	5.2	0	0	6.8	8.3
Infiltration of malignancy	3.8	0	2.9	0	9.1	3.8
Metabolic disorders	0	0	2.9	0	0	0.5
Postoperative	0	1.7	0	0	2.3	0.9
Miscellaneous	8.9	8.5	5.9	0	4.5	7.4

†Disease groups of acute liver failure shown in Methods. ‡"Indeterminate" means the etiology was uncertain despite sufficient examinations, and "unclassified" means uncertain etiology due to insufficient examinations.

Table 4 Diagnostic criteria for acute liver failure in Japan (2011)

Patients showing prothrombin time values of 40% or less of the standardized values, or international normalized ratios (INRs) of 1.5 or more due to severe liver damage within 8 weeks of the onset of disease symptoms are diagnosed as having "acute liver failure", where the liver function prior to the current onset of liver damage is estimated to be normal based on blood laboratory data and imaging examinations. "Acute liver failure" is classified into "acute liver failure without hepatic coma" and "acute liver failure with hepatic coma"; no or grade I hepatic encephalopathy is present in the former type, while grade II or more severe hepatic encephalopathy is found in the latter type. "Acute liver failure with hepatic coma" is further subclassified into two disease types; the "acute type" and "subacute type", respectively, with grade II or more severe hepatic encephalopathy developing within 10 days or between 11 and 56 days after the onset of disease symptoms, respectively, in the two types.

Note 1: Hepatitis B virus (HBV) carriers and autoimmune hepatitis patients showing acute exacerbation of hepatitis in the normal liver are included under the disease entity of "acute liver failure". In the case of indeterminate previous liver function, the patients with both etiologies are diagnosed as having "acute liver failure" when no liver function impairment preceding the exacerbation of the liver injury can be confirmed.

Note 2: In general, alcoholic hepatitis develops in patients with chronic liver diseases caused by habitual alcohol consumption. Thus, patients with alcoholic hepatitis are excluded from the disease entity of "acute liver failure". However, patients with fatty liver caused by alcohol intake or metabolic syndrome, including obesity, are diagnosed as having "acute liver failure" if etiologies other than habitual alcohol consumption are responsible for the acute injury in the liver, in the absence of prior impairment of liver function.

Note 3: Patients without histological evidence of hepatitis, such as inflammatory lymphocytic infiltration, are included under the disease entity of "acute liver failure". Thus, patients with liver damage caused by drug toxicity, circulatory disturbance or metabolic disease and acute fatty liver of pregnancy are diagnosed as having "acute liver failure," while they are excluded from the disease entity of "fulminant hepatitis". In contrast, patients with liver injury caused by viral infection, autoimmune hepatitis and drug allergy-induced hepatitis are included under the disease entities of "fulminant hepatitis" as well as "acute liver failure".

Note 4: The severity of hepatic encephalopathy is diagnosed depending on the classification presented in the Imuyama Symposium in 1972 (Table 5). Also, hepatic encephalopathy developing in pediatric and infantile patients is classified according to the criteria proposed by the 5th Workshop on Pediatric Liver Diseases in 1988 (Table 6).

Note 5: The etiology of "acute liver failure" is classified according to the criteria proposed by the Intractable Liver Diseases Study Group of Japan at 2002, with some modifications (Table 7).

Note 6: Patients showing prothrombin time values of less than 40% of the standardized values or INRs of 1.5 or more and grade II or more severe hepatic coma between 8 and 24 weeks of the onset of disease symptoms are diagnosed as having late-onset hepatic failure (LOHF), as a disease related to "acute liver failure".

are also included in the disease entity of "acute liver failure", while acute-on-chronic liver injuries, such as liver injury caused by alcohol, are excluded. Acute liver failure patients are classified into those with and without hepatic coma, depending on the severity of the hepatic encephalopathy, and "acute liver failure with hepatic coma" is further subclassified into two disease types, the "acute type" and the "subacute type". To clarify the concept of "acute liver failure" in Japan, five items are described in the footnote of the diagnostic criteria.

DISCUSSION

TO ESTABLISH THE diagnostic criteria for "acute liver failure" in Japan, two types of nationwide surveys were performed; the survey of commercial kits used for measurement of the prothrombin time used at institutions to which hepatology specialists were affiliated and the survey of acute liver failure patients who were excluded from the disease entities of fulminant hepatitis and LOHF. The former survey revealed that 16 commercial kits were used, and the INRs corresponding to 40% of the standardized values differed among the kits (range, 1.6 and 2.12), suggesting that an INR of 1.5 or more was a suitable cutoff value to include all patients previously diagnosed as having fulminant hepatitis or LOHF in the novel disease entity of "acute liver failure". On the other hand, the latter survey demonstrated that patients with acetaminophen-induced toxic liver injury, the most frequent cause of acute liver failure in Europe and the United States, were seldom found in Japan. In contrast, alcoholic liver injury was observed frequently among patients showing prolongation of the prothrombin time and/or grade II or more severe hepatic encephalopathy. The clinical features of these patients,

Table 5 Classification of hepatic encephalopathy depending on the grading of hepatic come in adult patients proposed by the inuyama symposium in 1972

The grade of coma	Psychiatric disorders	Reference items
I	• Inversion of sleep pattern • Euphoria and/or occasional depression • Sloppy attitude with Shortened attention span	Recognized retrospectively in most cases
II	• Disorientation for time or place and confusion of objects • Inappropriate behaviors, such as to throwing away money or discarding cosmetics • Occasional somnolent tendency; able to open eyes and respond appropriately to questions • Makes impolite remarks, but follows doctors' instructions	Excitation state and incontinence of urine and service are absent, but lapping tremor is found on physical examination
III	• State of excitation and/or delirium showing defiant behavior • Somnolent tendency; sleeping most of the time • Opens eyes in response to stimulation, but cannot follow the instructions of doctors, except for simple orders	Flapping tremor is observed, and the extent of disorientation is severe
IV	• Coma; complete loss of consciousness • Response to painful stimuli	Brushes off hands and/or frowns in response to stimuli
V	• Deep coma • No response to painful stimuli	

however, differed from those of the patients with fulminant hepatitis, since liver damage in alcoholic liver disease patients develops in an acute-on-chronic liver disease pattern. Also, the survey revealed that the most frequent cause of death was complications of liver disease, but not the liver failure itself, in most patients with etiologies not listed among the etiologies of fulminant hepatitis or LOHF.

Based on these observations, "acute liver failure" in Japan is defined as an acute liver disease associated with prolongation of the prothrombin time, with an INR of 1.5 or more. To confirm the correspondence between the present and previous criteria, "prothrombin time values of 40% or less of the standardized values" was also used as a cutoff to define the patients with acute liver failure. Consequently, patients without hepatic encephalopathy may also be included in the disease entity of acute liver failure, if they show an INR of 1.5 or more. Thus, acute liver failure patients are classified into those with and without hepatic coma, and acute liver failure with hepatic coma is further subdivided into two disease types, namely, the "acute type" and the "subacute type," according to the interval from the onset of symptoms to the development of hepatic encephalopathy, similarly to the case for fulminant hepatitis.[1,4]

Regarding the etiology of acute liver failure, patients without histological evidence of inflammation in the

Table 6 Classification of hepatic encephalopathy depending on the grading of hepatic coma in pediatric and infantile patients as proposed in the 5th workshop on pediatric liver diseases in 1988

Grade of coma	Pediatric	Infantile
I	Low-spirited from before (poor activity)	Does not laugh aloud
II	Obedient attitude with somnolent tendency Disorientation for time or place	Does not laugh even when dandled Cannot maintain eye contact with the mother (later than 3 months after birth)
III	Open eyes in response to loud voice	
IV	Does not wake up in response to painful stimuli, but frowns and/or brushes off by his/her hands	
V	No response to painful stimuli	

Table 7 Classification of etiologies of acute liver failure modified from the criteria proposed by the Intractable Liver Diseases Study Group of Japan in 2002

- I. Viral infection
  - 1 Hepatitis A virus (HAV)
  - 2 Hepatitis B virus (HBV)
    - (1) Transient infection
    - (2) Acute exacerbation in HBV carrier*
      - i. Inactive carrier, without drug exposure
      - ii. Reactivation in inactive carrier by immunosuppressant and/or anticancer drugs
      - iii. Reactivation in transiently infected patients by immunosuppressant and/or anticancer drugs (de novo hepatitis)
    - (3) Indeterminate infection patterns
  - 3 Hepatitis C virus (HBV)
  - 4 Hepatitis E virus (HEV)
  - 5 Other viruses
- II. Autoimmune hepatitis
- III. Drug-induced liver injuries
  - 1. Drug allergy-induced liver injury
  - 2. Drug toxicity-induced liver injury
- IV. Circulatory disturbance
- V. Infiltration of the liver by malignant cells
- VI. Metabolic diseases
- VII. Liver injuries after liver resection and transplantation
- VIII. Miscellaneous etiologies
- IX. Indeterminate etiology despite sufficient examinations
- X. Unclassified due to insufficient examinations

Patients with etiologies I, II and III-1 are diagnosed as having "fulminant hepatitis" as well as "acute liver failure", whereas those with etiologies III-2 and IV to VIII are diagnosed as having "acute liver failure", but excluded from disease entity of "fulminant hepatitis". Diagnostic criteria for classification of etiology based on laboratory data should be established in the future.
Serum HBs antigen-negative patients following transient infection with HBV are classified as HBV carriers, in which HBV reactivation can be induced by immunosuppressant and/or anticancer drugs, but the significance of this causative etiology needs to be evaluated further.

liver, such as those with the disease caused by drug toxicity, circulatory disturbance or metabolic disease, were included under the disease entity of acute liver failure. In contrast, patients showing impaired liver function due to underlying chronic liver diseases before the worsening of the liver damage were excluded from the disease entity of acute liver failure. Thus, alcoholic liver disease patients were excluded from the disease entity, since they showed clinical features consistent with acute-on-chronic liver disease. However, patients with underlying chronic liver diseases such as fatty liver due to alcohol intake or metabolic diseases, including obesity, were included in the disease entity of acute liver failure, when the liver function impairment was retrospectively estimated to be minimal or absent prior to the current exacerbation of liver damage, since the incidence of metabolic syndrome has been increasing in the Japanese population. The patients with autoimmune hepatitis were defined similarly to those with underling fatty liver, because the presence of chronic liver disease preceding the hepatitis exacerbation is uncertain in most of these patients. On the other hand, patients with liver injury caused by viral infection, autoimmune hepatitis and drug allergy-induced hepatitis are included under the disease entities of "fulminant hepatitis" as well as "acute liver failure". The significance of diagnostic criteria for fulminant hepatitis should be further evaluated in the future.

In addition, the diagnostic criteria for LOHF as a disease related to "acute liver failure". LOHF was defined as grade II or more severe hepatic encephalopathy developing between 8 and 24 weeks of the onset of symptoms.[1,4] However, in the present criteria, patients with LOHF were defined as those showing INRs of 1.5 or more as well as prothrombin time values of 40% or less of the standardized values. Thus, patients without histological evidence of hepatitis are also included in the disease entity of LOHF, similar to the case of acute liver failure. On the other hand, the disease entity of "acute hepatitis severe type", in which

patients show no or grade I hepatic encephalopathy despite having prothrombin time values of 40% or less as compared to the standardized values, was excluded from the footnote of the present criteria, since patients classified under such a disease entity can also be diagnosed as having "acute liver failure without hepatic encephalopathy".

In conclusion, the diagnostic criteria for "acute liver failure" in Japanese patients were established. A nationwide survey of "acute liver failure" will be conducted by the Intractable Hepato-Biliary Diseases Study Group of Japan after 2011, based on these novel criteria. Also, the significance of the diagnostic criteria in Japan should be further evaluated in relation to the criteria in Europe and the United States.

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Original Article

Novel scoring system as a useful model to predict the outcome of patients with acute liver failure: Application to indication criteria for liver transplantation

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Aim: In Japan, the indication for liver transplantation in patients with acute liver failure (ALF) is currently determined according to the guideline published in 1996. However, its predictive accuracy has fallen in recent patients. Thus, we attempted to establish a new guideline.

Methods: The subjects were 1096 ALF patients enrolled in a nationwide survey. All patients showed a prothrombin time <40% of the standardized value and grade II or more severe hepatic encephalopathy. A multiple logistic regression analysis and receiver operating characteristic analysis were performed in 698 patients seen between 1998 and 2003 to identify significant parameters determining the outcome of patients. The extracted parameters were graded as numerical scores. An established scoring system was validated in patients seen between 2004 and 2008.

Results: Six parameters were identified and graded as 0, 1 and/or 2; the interval between disease onset and development of hepatic encephalopathy, prothrombin time, serum total bilirubin concentration, the ratio of direct to total bilirubin concentration, peripheral platelet count and the presence of liver atrophy. When the prognosis of the patients with total score of 5 or more was judged as "death", the predictive accuracy was 0.80 with sensitivity, specificity, positive predictive value and negative predictive value greater than 0.70. The values were similarly high in patients for validation.

Conclusion: Novel scoring system for predicting the outcome of ALF patients may be useful to determine the indication of liver transplantation, since the system showed high predictive accuracy even after validation.

Key words: acute liver failure, fulminant hepatitis, guideline, indication criteria, liver transplantation, outcome prediction

INTRODUCTION

ACUTE LIVER FAILURE is a disease entity characteristic with extensive destruction of liver parenchyma by hepatitis virus infection and other causes, and is typically represented by fulminant hepatitis. Although the outcome may differ depending on the etiology of acute liver failure, survival rates of patients receiving conventional medical care are generally low in cases with impaired liver regeneration. Hepatitis patients are diagnosed as fulminant hepatitis in Japan if grade II or deeper hepatic encephalopathy develops within 8 weeks of the onset of hepatitis symptoms due to severe abnormality of the liver function with prothrombin time lower than 40% of the standardized value. Fulminant hepatitis is further classified into two subtypes according to clinical

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course; acute type with hepatic encephalopathy developing within 10 days of disease onset and subacute type with hepatic encephalopathy at 11 days or later.[1,2] In addition, late onset hepatic failure (LOHF) is defined as a related disease of fulminant hepatitis, in which hepatic encephalopathy develops between 8 and 24 weeks after the onset of hepatitis symptoms.[2] Fulminant hepatitis in Japan is defined as acute liver failure with histological appearance of hepatic inflammation, such as lymphocyte infiltration in the liver. Thus, the etiology of fulminant hepatitis comprises viral hepatitis including persistent hepatitis B virus (HBV) carriers, autoimmune hepatitis, drug-induced/allergic hepatitis, and hepatitis with indeterminate etiologies, but excludes drug-induced/toxic liver damage, acute fatty liver in pregnancy, postoperative liver damage and ischemic liver damage. However, in Europe and the United States, the latter causes are included in the disease entity of acute liver failure, formerly called fulminant hepatic failure. Thus, for example, acetaminophen-induced liver damage is included in acute liver failure in Europe and the United States, while it is excluded from the disease entity of fulminant hepatitis in Japan.[3] Considering such differences of the definition and diagnostic criteria between fulminant hepatitis in Japan and acute liver failure in the United States and Europe, the guidelines in the latter countries to determine the indication of liver transplantation for acute liver failure are not directly applicable to fulminant hepatitis in Japan.

It is accepted worldwide that liver transplantation is the most effective therapeutic modality for patients with acute liver failure. In Japan, indication criteria for liver transplantation in patients with fulminant hepatitis were defined in 1996, as a two-step outcome prediction scoring system, by the Acute Liver Failure Study Group of Japan (Table 1).[4,5] According to this guideline, the outcome of fulminant hepatitis patients is predicted at the onset of grade II or more severe hepatic encephalopathy based on five parameters: age of patient, the interval between occurrence of hepatitis symptoms and development of hepatic encephalopathy, prothrombin time, serum total bilirubin concentration and the ratio of the serum direct to total bilirubin concentration. Then, in patients undergoing intensive medical care including artificial liver support, their prognosis is reassessed 5 days later, according to the extent of improvement of hepatic encephalopathy and prothrombin time. This guideline was prepared based on the clinical findings in fulminant hepatitis patients seen between 1988 and 1992, and was considered to be useful, since the predictive accuracy was found to be 83% in a prospective analysis conducted in patients seen between 1993 and 1995.[4] However, the predictive accuracy of the guideline fell in patients with fulminant hepatitis seen between 1998 and 2003; 68% and 78% in the acute and subacute types, respectively, and the values did not improve following reassessment at 5 days later.[6]

Table 1 Guideline to determine the indications for liver transplantation in patients with fulminant hepatitis by the Acute Liver Failure Study Group of Japan in 1996

Patients may be registered as recipients of liver transplantation when at least two of the five criteria are satisfied at the time of onset of Grade II or more severe hepatic encephalopathy.

1 Age ≥45 years.
2 Interval from the appearance of the initial symptoms to the development of hepatic encephalopathy ≥11 days.
3 Prothrombin time <10% of the standardized value.
4 Serum bilirubin concentration ≥18.0 mg/dL.
5 Ratio of the direct to total bilirubin concentration <0.67.

If liver transplantation cannot be performed within 5 days and intensive medical therapy, including artificial liver support, is undertaken, the prognosis of the patients is evaluated again. If both of the following two criteria are positive at 5 days after the onset of hepatic encephalopathy, the patients are re-predicted as "alive" and excluded from the candidate list for liver transplantation.

1 The hepatic encephalopathy shows improvement to Grade I or less or attenuation by two more grades.
2 Prothrombin time improves to over 50% of the standardized value.

English version of this guideline was published in Mochida *et al.*[5]

To improve the predictive accuracy of indication criteria for liver transplantation in patients with fulminant hepatitis, the Study Group of Intractable Hepatobiliary Diseases supported by the Ministry of Health, Labor, and Welfare of Japan organized a task force in 2006. The task force first analyzed the database obtained from patients with fulminant hepatitis and LOHF seen between 1998 and 2003 in Japan to establish the novel scoring system to predict the outcome of the patients. Then, the established system was evaluated in the patients seen between 2004 and 2008. In the present paper, we report on the usefulness of this novel scoring system. We state here that the new system is intended for use in a general cohort of acute liver failure, but is actually organized on the database of registered patients with fulminant hepatitis and LOHF. Thus, validation of

the system for acute liver failure due to other etiologies as described earlier awaits future study.

METHODS

Patients

THE STUDY SUBJECTS are 1096 patients with acute liver failure who were enrolled in the nationwide survey by the Intractable Hepato-Biliary Disease Study Group of Japan between 1999 and 2008 (formerly the Intractable Liver Diseases Study Group of Japan before 2003). All of the patients showed grade II or more severe hepatic encephalopathy and prothrombin time of less than 40% of the standardized value and were admitted to 610 hospitals of Japan specializing in hepatology between 1998 and 2008. The patients consisted of three disease types; 505 and 449 patients, respectively, with acute and subacute types of fulminant hepatitis and 88 patients with LOHF. They were divided into two cohorts; 698 patients (316, 318 and 64 patients, respectively, with acute and subacute types of fulminant hepatitis and LOHF) seen between 1998 and 2003 (the estimation cohort) and 394 patients (189, 191 and 24 patients, respectively, of each disease type) seen between 2004 and 2008 (the validation cohort). From both cohorts, the patients with incomplete records and those treated with liver transplantation were excluded. Thus, the estimation cohort included 421 patients (201 and 178 patients, respectively, with acute and subacute types of fulminant hepatitis and 41 patients with LOHF) and the validation cohort recruited 231 patients (125, 95 and 11 patients, respectively, in each disease type).

Etiologies of hepatitis in the estimation and validation cohorts are given in Table 2. Demographic and clinical features of patients in each cohort are shown in Tables 3 and 4, respectively. These features did not differ between the two cohorts, except that the ages of the patients were greater in the validation cohort than in the estimation cohort. The survival rates of patients were equivalent between two cohorts; 37.4% in the estimation cohort and 37.7% in the validation cohort.

Identification of prognostic factors responsible for the outcome of patients with fulminant hepatitis and LOHF in the estimation cohort

First, univariate logistic analysis was performed in patients of the estimation cohort to identify possible prognostic factors among demographic and clinical features at the onset of grade II or more severe hepatic encephalopathy as follows. (i) *Demographic features*; sex and age of patients, the types of disease (acute and subacute types of fulminant hepatitis and LOHF), the interval (days) between the onset of hepatitis symptoms and the development of hepatic encephalopathy. (ii) *Symptoms*; fever of 37.5°C or more, convulsion, tachycardia, disappearance of liver dullness on physical examination, flapping tremor, hepatic odor and edema. (iii) *Laboratory parameters*; prothrombin time (%), hepaplastin test (%), antithrombin III activity (%), serum concentrations of albumin (g/dL) and total and direct bilirubin (mg/dL), the ratio of direct to total bilirubin concentration, serum levels of aspartate aminotransferase (AST: IU/L) and alanine aminotransferase (AST: IU/L), serum α-fetoprotein concentration (ng/mL), blood ammonia concentration (μg/dL), plasma concentration of hepatocyte growth factor (HGF: ng/mL), peripheral platelet and white blood cell counts (/mm^3). (iv) *Imaging*; liver atrophy diagnosed by ultrasound sonography and/or computed tomography/magnetic resonance imaging (CT/MRI).

Extracted factors were subjected to multivariate logistic analyses through a stepwise elimination manner. Then a receiver operating characteristic (ROC) curve was constructed for each significant variable.

Table 2 Etiologies of fulminant hepatitis and late onset hepatic failure (LOHF) in the estimation cohort and validation cohort

	Estimation cohort 1998–2003	Validation cohort 2004–2008
HAV	33	15
HBV (acute onset)	104	51
HBV (career)	65	33
HBV (unclassified)	9	16
HCV	8	3
Other Virus	3	5
AIH	26	23
Drug	35	33
Undetermined	132	49
No record	6	3
Total	421	231

Data are expressed as the number of patients.
AIH, autoimmune hepatitis; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

Scoring of prognostic factors and predicted mortality of patients with fulminant hepatitis and LOHF in the estimation and validation cohorts

The grading of variables was determined as numerical scores based on the inflection points of each ROC curve.

Table 3 Demographic and clinical features of patients with fulminant hepatitis and late onset hepatic failure (LOHF) seen between 1998 and 2003 (estimation cohort)

	Total ($n = 421$)	Dead patients ($n = 260$)	Surviving patients ($n = 161$)
Sex (Male : Female)	218:202:(1)†	148:111:(1)†	70:91
Age	48.6 ± 16.3‡	53.2 ± 14.8**	41.3 ± 16.0
HBV Carrier	15.2% (64/421)	18.8%** (49/260)	9.3% (15/161)
Disease Type (FHA : FHS : LOHF)	201:178:41	86:138:36**	115:40:5
HGF (ng/mL)	6.0 ± 11.4	7.6 ± 13.9*	3.9 ± 6.0
TB (mg/dL)	14.0 ± 9.1	16.6 ± 9.6**	9.7 ± 6.2
D/T ratio	0.63 ± 0.13	0.62 ± 0.14**	0.66 ± 0.12
PT (%)	22.7 ± 12.6	22.5 ± 13.8*	23.5 ± 11.3
AT (%)	37.3 ± 20.3	35.9 ± 20.3*	41.5 ± 19.9
NH3 (μg/dL)	138.7 ± 82.8	151.6 ± 87.8**	118.1 ± 69.6
PLT (10^4/μL)	12.7 ± 7.7	12.1 ± 8.1*	13.6 ± 6.9
Liver Atrophy (present : absent)	265:156	210:50**	55:106
O-C (days)	21.2 ± 26.7	26.4 ± 29.3**	12.8 ± 19.2

*$P < 0.05$, **$P < 0.01$ versus alive.
†A value in parenthesis means the number of patients with no record regarding the sex.
‡Values are expressed as mean ± standard deviation (SD).
AT, antithrombin III; D/T ratio, ratio of direct to total bilirubin concentrations; FHA, acute type of fulminant hepatitis; FHS, subacute type of fulminant hepatitis; HBV, hepatitis B virus; HGF, hepatocyte growth factor; O-C, intervals between hepatitis onset and hepatic encephalopathy development; PLT, platelet; PT, prothrombin time; TB, total bilirubin.

The total scores were calculated in each patient belonging to the estimation cohort, and the mortality rates were evaluated depending on total scores. Then, ROC analysis was performed again to identify the cut-off value of the total score that can discriminate sharply between survived and dead patients. Finally, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and predictive accuracy of the established scoring system were calculated when the predicted outcome of patients with the total score greater than the cut-off value was judged as "death".

Predictive accuracies of the established system were confirmed similarly in the validation cohort.

Statistical analysis

All statistical analyses were performed with JMP v7.0 for Macintosh (SAS Institute Inc., Cary, NC, USA). Univariate analyses were performed with analysis of variance (ANOVA) and χ^2 test. Multivariate analyses were performed by multiple logistic regression analysis with stepwise selection.

RESULTS

Prognostic factors responsible for the outcome of patients with fulminant hepatitis and LOHF

UNIVARIATE LOGISTIC ANALYSIS revealed 18 variables including demographic features and clinical characteristics at the appearance of grade II or more severe hepatic encephalopathy may affect the mortality of the patients; age of patients, the interval between disease onset and the development of hepatic encephalopathy, presence of tachycardia and edema, disappearance of liver dullness on physical examination and presence of liver atrophy on imaging examination, serum concentrations of albumin and total bilirubin, the ratio of direct to total bilirubin concentration, serum levels of AST and ALT, blood ammonia level, plasma HGF concentration, prothrombin time, hepaplastin test, antithrombin III activity and peripheral platelet count. These factors were subjected to multivariate logistic analysis with stepwise elimination manner, and 10 variables were identified as significant as shown in Table 5. At this step,

Table 4 Demographic and clinical features of patients with fulminant hepatitis and late onset hepatic failure (LOHF) seen between 2004 and 2008 (validation cohort)

	Total ($n = 231$)	Dead patients ($n = 144$)	Surviving patients ($n = 87$)
Sex (Male : Female)	120:111	74:70	46:41
Age	54.7 ± 15.0†	59.8 ± 12.2**	46.3 ± 15.6
HBV Carrier	14.2% (33/231)	19.4% (28/144)	5.7% (5/87)
Disease Type (FHA : FHS : LOHF)	125:95:11	61:74:9**	64:21:2
HGF (ng/mL)	6.0 ± 9.2	7.1 ± 10.4	3.2 ± 3.6
TB (mg/dL)	13.7 ± 8.9	16.6 ± 9.3**	8.8 ± 5.3
D/T ratio	0.64 ± 0.14	0.64 ± 0.13	0.63 ± 0.16
PT (%)	24.5 ± 12.7	22.0 ± 12.4**	28.4 ± 12.4
AT (%)	38.2 ± 20.4	34.4 ± 21.1*	44.3 ± 17.7
NH3 (μg/dL)	162.0 ± 141.8	191.1 ± 168.8**	116.4 ± 60.7
PLT (10^4/μL)	12.6 ± 7.2	11.5 ± 6.9**	14.3 ± 7.2
Liver Atrophy (Present/absent)	146:85	114:30**	32:50
O-C (days)	15.9 ± 17.0	19.0 ± 18.5**	10.6 ± 12.2

*$P < 0.05$, **$P < 0.01$ versus alive.
†Values are expressed as mean ± standard deviation (SD).
AT, antithrombin III; D/T ratio, ratio of direct to total bilirubin concentrations; FHA, acute type of fulminant hepatitis; FHS, subacute type of fulminant hepatitis; HBV, hepatitis B virus; HGF, hepatocyte growth factor; O-C, intervals between hepatitis onset and hepatic encephalopathy development; PLT, platelet; PT, prothrombin time; TB, total bilirubin.

"age of patients" was excluded from the list of candidate variables in order to facilitate the system to be available in pediatric patients. Then ROC curve was constructed for each variable, and six variables with the greatest area under the curve (AUC) were identified; the interval between disease onset and the development of hepatic encephalopathy, prothrombin time, serum concentration of total bilirubin, the ratio of direct to total bilirubin concentration, peripheral platelet count, and liver atrophy.

Table 5 Prognostic factors to affect the outcome of patients with fulminant hepatitis and late onset hepatic failure (LOHF): multivariate logistic analysis in those seen between 1998 and 2003 (estimation cohort)

	Odds ratio†	(95% confidence interval)	*P*-value
Liver atrophy	9.777		<0.0001
TB	1.0993	(1.043–1.168)	0.0009
D/T ratio	0.000446	(0.0001146–0.081412)	0.0062
NH3	1.007	(1.002–1.014)	0.0098
Age	1.0654	(1.010–1.136)	0.0113
PT%	0.9773	(0.959–0.995)	0.0115
HGF	1.1837	(1.049–1.374)	0.0139
O-C	1.0687	(1.014–1.141)	0.0270
ALB	0.0409	(0.129–0.906)	0.0312
PLT	0.9648	(0.931–0.999)	0.0489

†Odds ratio of dead patients to survived patients in relation to the presence or absence of liver atrophy and a unit increase of each continuous parameter.
ALB, albumin; D/T ratio, ratio of direct to total bilirubin concentration; HGF, hepatocyte growth factor; O-C, the interval between hepatitis onset and the development of hepatic encephalopathy; PLT, platelet; PT, prothrombin time; TB, total bilirubin.

Table 6 Scores for Predictive Variables Affecting the Mortality of Patients with Fulminant Hepatitis and late onset hepatic failure (LOHF)

Score	0	1	2
O-C (days)	≤5	6–10	11≤
PT (%)	20<	5< ≤20	≤5
TB (mg/dL)	<10	10≤ <15	15≤
D/T ratio	0.7≤	0.5≤ <0.7	<0.5
PLT (104/μL)	10<	5< ≤10	≤5
Liver atrophy	Absent	Present	

D/T ratio, ratio of direct to total bilirubin concentrations; O-C, the interval between hepatitis onset and the development of hepatic encephalopathy; PLT, platelet; PT, prothrombin time; TB, total bilirubin.

Scoring system to predict the possible outcome of patients with fulminant hepatitis and LOHF

Variables extracted through ROC curve analysis were graded as shown in Table 6, according to the inflection points of each curve. The interval between hepatitis onset and the development of hepatic encephalopathy, prothrombin time, serum concentration of total bilirubin, the ratio of direct to total bilirubin concentration and peripheral platelet count were classified into three grades (0, 1 and 2), and liver atrophy into two grades (0 and 1).

As shown in Table 7, the mortality rates rose in relation to total scores calculated in patients seen between 1998 and 2003 (estimation cohort). When the predictive outcome of patients showing total scores of 5 or more was judged as "death", PPV and NPV of the system were 0.84 and 0.70, respectively (Table 8), suggesting that total scores of 5 is sufficient enough as a cut-off value that can discriminate between dead and survived patients. The scoring system with such cut-off value showed sensitivity and specificity of 0.80 and 0.76, respectively, and resulted in predictive accuracy of 0.78 in patients in the estimation cohort. Predictive accuracies did not differ depending on the disease types; 0.75 in patients with acute type of fulminant hepatitis and 0.87 in those with subacute type of fulminant hepatitis.

Table 7 The outcome of patients with fulminant hepatitis and late onset hepatic failure (LOHF) seen between 1998 and 2003 (estimation cohort) depending on total scores calculated through established scoring system

Total scores	Mortality (%)	FHA/FHS/LOHF
9≤	9/10 (90.0%)	2/4/4
8	26/27 (96.3%)	2/20/5
7	42/46 (91.3%)	10/30/6
6	71/83 (85.5%)	20/52/11
5	59/80 (73.8%)	26/42/12
4	31/55 (56.3%)	32/22/1
3	12/50 (24.0%)	44/4/2
2	8/40 (20.0%)	35/5/0
1	2/25 (8.0%)	25/0/0
0	0/5 (0.0%)	5/0/0

FHA, acute type of fulminant hepatitis; FHS, subacute type of fulminant hepatitis.

Table 8 Accuracies of established scoring system in patients with fulminant hepatitis and late onset hepatic failure (LOHF) seen between 1998 and 2003 (estimation cohort) when predictive outcome of patients showing total scores of 5 or more are diagnosed as "death"

	Total scores		
	≥5	<5	Total
Number of patients			
Dead patients	207	53	260
Surviving patients	39	122	161
Total	246	175	421
Mortality	84.1%	30.3%	61.8%
The accuracies			
Positive predictive value (PPV)	207/246		0.84
Negative predictive value (NPV)	122/175		0.70
Sensitivity	207/260		0.80
Specificity	122/161		0.76
Predictive accuracy (PA)	(207+122)/421		0.78

The accuracies of the established scoring system were validated in patients with fulminant hepatitis and LOHF seen between 2004 and 2008 (validation cohort). As shown in Table 9, the mortality rate of patients in each total score was almost equivalent to that obtained in analysis with patients in the estimation cohort. Thus, predictive accuracy through analysis in the validation cohort was 0.75 with sensitivity, specificity, PPV and NPV of 0.75, 0.80, 0.86 and 0.65, respectively (Table 10).

DISCUSSION

LIVER TRANSPLANTATION IS regarded worldwide as the most effective therapeutic procedure for patients with end-stage liver diseases including acute liver

Table 9 The outcome of patients with fulminant hepatitis and late onset hepatic failure (LOHF) seen between 2004 and 2008 (validation cohort) depending on total scores calculated through established scoring system

Total scores	Mortality (%)	FHA/FHS/LOHF
9≤	4/4 (100.0%)	0/3/1
8	9/9 (100.0%)	1/6/2
7	26/30 (86.7%)	9/20/1
6	35/39 (89.7%)	9/29/1
5	33/42 (78.6%)	18/19/5
4	21/39 (53.8%)	28/10/1
3	10/30 (33.3%)	22/8/0
2	4/26 (15.4%)	26/0/0
1	2/8 (25.0%)	8/0/0
0	0/4 (0.0%)	4/0/0

FHA, acute type of fulminant hepatitis; FHS, subacute type of fulminant hepatitis.

failure. Japanese Society for the Study of Liver Transplantation revealed that survival rate at 1 year after liver transplantation was 72.7% in patients with acute liver failure,[7] while conventional medical care yielded insufficient prognosis in such patients; survival rates were 54.0% and 24.0%, respectively, in patients with fulminant hepatitis of acute and subacute types and 15.0% in LOHF patients according to the nationwide survey by the Study Group of Intractable Hepatobiliary Diseases.[8] In general, in Japan, patients with acute liver failure visit clinics or hospitals at the onset of hepatitis symptoms and derangement of liver function was diagnosed by physicians specialized in general medicine. Next, the patients were transferred to hospitals with specialists in the fields of hepatology and emergency medicine around the periods of the development of hepatic encephalopathy. Conventional medical care including artificial liver support with plasma exchange and hemodiafiltration was performed, and then the patients were introduced to transplant surgeons regarding the indication of liver transplantation. Thus, the simple criteria to predict the outcome of patients with fulminant hepatitis and LOHF with sufficient accuracies are required to facilitate communication among general physicians, hepatologists and transplant surgeons.

Table 10 Accuracies of established scoring system in patients with fulminant hepatitis and late onset hepatic failure (LOHF) seen between 2004 and 2008 (validation cohort) when predictive outcome of patients showing total scores of 5 or more are diagnosed as "death"

	Total scores		
	≥5	<5	Total
Number of patients			
Dead patients	107	17	124
Surviving patients	37	70	107
Total	144	87	231
Mortality	74.3%	19.5%	53.7%
The accuracies			
Positive predictive value (PPV)	107/144		0.75
Negative predictive value (NPV)	70/87		0.80
Sensitivity	107/124		0.86
Specificity	70/107		0.65
Predictive accuracy (PA)	(107+70)/231		0.77

In Europe and the United States, the indication of liver transplantation in patients with acute liver failure has been determined according to the guideline proposed by King's Collage Hospital[9] and Beaujon Hospital.[10] In addition, a scoring system of model for end-stage liver disease (MELD), initially designed for patients with chronic liver failure, has recently been applied also to those with acute liver failure.[11] However, these guidelines are not directly applicable to patients with fulminant hepatitis and LOHF in Japan, since social environment as well as demographic and clinical features of the patients differ among Japan, Europe and the United States; for example liver transplantation with brain death-related donor is hardly available and artificial liver support is routinely performed in Japan. Thus, novel guidelines should be established for Japanese patients with fulminant hepatitis and LOHF instead of the previous guideline proposed by the Acute Liver Failure Study Group in Japan at 1996,[4] which shows decline of predictive accuracy when applied to recent patients.[5]

In the present paper, a novel scoring system to predict the outcome of patients with fulminant hepatitis and LOHF was established based on demographic and clinical features of patients seen between 1998 and 2008. The predictive mortality rates were estimated through six variables at the occurrence of grade 2 or more severe hepatic encephalopathy; the interval between the onset of hepatitis symptoms and the development of hepatic encephalopathy, prothrombin time, serum concentration of total bilirubin, the ratio of direct to total bilirubin concentration, peripheral platelet count and presence of liver atrophy on imaging. When total scores were calculated through six variables in patients belonging to the estimation cohort, the mortality rate was 84.1% in those with scores of 5 or more, while it was 30.3% in those with scores of 4 or less. Thus, the cut-off value of total scores to discriminate possible dead