DISCUSSION

Although clinical signs in small-for-size grafts sometimes occur, most patients with small-for-size grafts recover from small-for-size graft syndrome. The causes of differences between survivors and those with graft failure are unknown. In this study, we investigated the time course of hepatic hemodynamics in patients with small-for-size grafts. Because of the small number of patients with graft failure, statistical analysis was difficult. However, definitive differences were seen in hepatic hemodynamics between survivors and patients with graft failure. The hemodynamic features in the patients with graft failure were (1) extremely increased PVPV on postoperative day 1; (2) rapidly deteriorated PVPV in the early postoperative period; (3) reciprocally increased HAPSV; and (4) increased SAPI indicating portal hypertension. In contrast, each hemodynamic parameter of survivors with small-for-size grafts was stable during the early postoperative days.

In this study, PVPV was over 90 cm/sec in patients with graft failure. The PVPV in normal subjects is generally around 10 cm/s in the umbilical portion, and even in patients with a right-portal embolization, it is around 20 cm/sec in the umbilical portion.[17] The PVPV in LDLT with graft failure is far higher, at over 90 cm/sec. Marcos et al[5] reported that the postoperative PVPV in a small graft (ratio, 0.9%) was significantly higher (115 cm/sec) than in larger grafts (ratio 1.2%; 50 cm/s). They indicated that this high shear stress may be one of the most important contributors to dysfunction of small-for-size grafts. Excessive portal flow and its effect on arterial flow may be responsible for the dysfunction and failure of small liver grafts.[18]

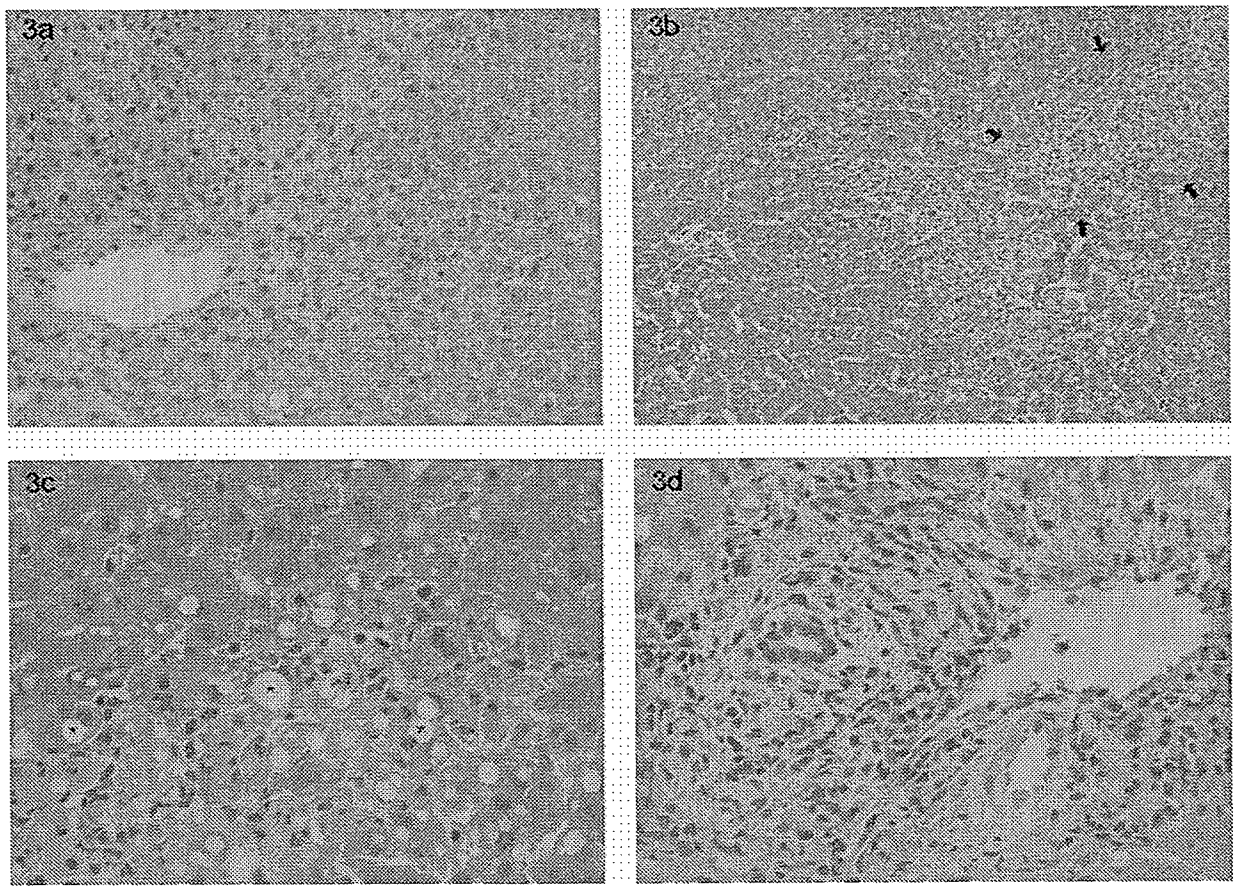

Fig 3a–d. Histologic findings. **a.** Patient 1 on postoperative day 1 (HE 200). There were no abnormal findings such as ischemic/reperfusion injury or rejection. **b, c, d.** Patient 1 on postoperative day 6 when hepatofugal portal flow occurred (HE 100, 400, 400, respectively). Mild sinusoidal dilatation but no sinusoidal congestion is seen in the lower left side in **b.** Submassive necrosis is seen in the upper right side and vacuolar change of hepatocytes (*asterisk*) around submassive necrosis (*arrow*) is seen in **b.** Vacuolar changes and cholestasis in hepatocyte cytoplasm are evident in **c** (*asterisk* indicates the typical vacuolar change). There were no signs of acute rejection in portal areas in **d.**

We also investigated the relation between the hemodynamic changes and histologic changes. There are few reports of the histology of small-for-size graft. Emond et al[19] reported that liver biopsies of small grafts were initially interpreted as demonstrating "preservation injury," a syndrome characterized by hepatocyte ballooning and steatosis, centrilobular necrosis, and parenchymal cholestasis. However, they could not account for the histologic changes of small-for-size grafts because they did not measure hemodynamic changes. In this study, the hemodynamic characteristics of critical small-for-size graft syndrome were (1) portal hyperperfusion immediately after LDLT, and (2) sequentially increasing portal resistance and portal hypertension indicated by deterioration of PVPV and high SAPI when critical graft injury occurred in the early postoperative period. Histologic analysis showed submassive necrosis with surrounding vacuolar changes. The relation between these histologic changes, especially vacuolar change and hepatic hemodynamics, was reported by Shibayama et al.[20–22] They reported that marked vacuolar change was seen in hepatocytes at a portal vein pressure of 17 cm H_2O in the rat isolated liver, and concluded that the development of vacuolar degeneration of hepatocytes is closely related to an increase in the intrasinusoidal pressure, but not to hypoxia. Portal hyperperfusion immediately after LDLT may cause these histologic changes. Sequentially increased portal resistance and portal hypertension indicated by deteriorated PVPV and high SAPI may be caused by these histologic changes. Particular attention should be paid to the immediate and serial portal pressure changes after transplantation. Adequate portal flow and sinusoidal pressure are needed for good hepatocyte regeneration.

We also consider, as in previous reports, that the effect of a portohepatic vein shunt on portal vein decompression may be an important factor to prevent graft injury after recirculation in an extremely small graft. In this study, patient 1, who had a major splenorenal shunt before LDLT, survived a long time after the critical hemodynamic change. It is likely that the splenorenal shunt played an advantageous role in portal decompression. Many authors have reported that portal vein decompression improves survival in partial liver transplantation.[23–26] Further clinical and experimental studies will be needed to elucidate this strategy for small-for-size grafts. The management of perioperative portal pressure by surgical or medical manipulation may be important.

In conclusion, portal hyperperfusion immediately after LDLT in small-for-size grafts and subsequent intrasinusoidal pressure elevation during the early postoperative period lead to histologic changes such as vacuolar change and submassive hepatocyte necrosis. The critically decreased vascular beds cause further intrasinusoidal pressure elevation finally leading to graft failure. Serial postoperative measurements of portal circulation including portal blood velocity and portal pressure, may play an important role in evaluating the best strategy for small-size grafts.[23–26]

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Noninvasive Evaluation of Graft Steatosis in Living Donor Liver Transplantation

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Background. Hepatic steatosis affects graft function as well as postoperative recovery of donors in living donor liver transplantation. Liver macrovesicular steatosis in living donors was assessed using quantitative X-ray computed tomography (CT) analysis and histological examination of intraoperative liver biopsy.

Methods. A total of 266 living donors with complete pretransplant CT data and intraoperative "time 0" biopsy were included in the study. Liver biopsy specimen obtained during donor operation was examined for macrovesicular steatosis and was classified as none; mild (30%); moderate (30%–60%); or severe (60%). Liver-to-spleen CT attenuation values ratio (L/S ratio) on noncontrast-CT was evaluated for its usefulness as an index of hepatic steatosis in comparison with other parameters including body mass index (BMI) and serum liver function tests (gamma-glutamyl transpeptidase, alanine aminotransferase, aspartate aminotransferase, cholinesterase, and total cholesterol) using receiver operating characteristic (ROC) analysis.

Results. Histological grade of macrovesicular steatosis was none in 198 patients (74.4%), mild in 50 (18.8%), moderate in 15 (5.7%), and severe in 3 (1.1%). The median L/S ratios for the respective histological grades were 1.20 (range: 1.00–1.46), 1.12 (0.83–1.37), 1.01 (0.74–1.21), and 0.90 (0.70–0.99) (P 0.0001). The ROC curve for L/S ratio was located closest to the upper left corner, and the area under the curve of L/S ratio was significantly larger than that of any other preoperative variables.

Conclusion. L/S ratio calculated from preoperative CT can be a useful tool to discriminate hepatic macrovesicular steatosis. Based on the present results, the optimal cut-off value for L/S ratio to exclude more than moderate steatosis would be 1.1.

Keywords: Liver-to-spleen CT attenuation values ratio, Receiver operating characteristic analysis, Macrovesicular steatosis, Living donor liver transplantation.

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In cadaveric liver transplantation (CLT), fatty infiltration of the liver is common among the brain-dead donor population. Most centers will use cadaveric grafts with up to 30% macrosteatosis (*1*), and there are reports of successful CLT with extensive hepatic microsteatosis (*2*). However, the presence of significant macrosteatosis (60%) has been associated with primary nonfunction (PNF) of the graft liver, a condition that is catastrophic to liver transplant recipients (*3–5*). In living donor liver transplantation (LDLT), graft steatosis is one of the risk factors for graft dysfunction, and it is thought that the presence of severe macrovesicular steatosis is an absolute contraindication for the use of that organ for transplantation (*6*). In addition, hepatic steatosis affects postoperative recovery of the living donor (*7*). It is therefore very important to accurately diagnose the grade of donor hepatic steatosis in preoperative donor evaluation.

Several methods, including abdominal ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), body mass index (BMI) [kilograms/(height in meters)], waist/hip ratio, and liver function tests, have been used for evaluating hepatic steatosis (*8–10*). While these modalities are useful for investigating liver diseases, liver biopsy is still essential for diagnosis of hepatic steatosis and is the gold standard for the majority of patients (*11, 12*). Although liver needle biopsy is considered a relatively safe procedure, it has been reported that up to 5% of patients require hospitalization after the procedure and the incidence of significant bleeding is 1% with a fatal outcome in 1 of 10,000 patients (*13, 14*). To minimize such complications of needle biopsy, a noninvasive method would be required to evaluate hepatic steatosis in living donors before donor surgery.

Noncontrast-CT is currently one of the best radiological techniques for diagnosing of hepatic steatosis. The purpose of this study was to evaluate the accuracy of liver-to-spleen CT attenuation values ratio (L/S ratio) on noncontrast-CT in comparison with BMI or serum liver function tests for predicting hepatic steatosis.

PATIENTS AND METHODS

Donor Selection

Selection criteria for living donors in our institute were in principal based on age (20 to 60 years), ABO-blood type

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compatibility, estimated graft size (greater than 1.0% of recipient body weight), and estimated residual liver volume (greater than 30% of the whole liver). Donor candidates with suspicion of hepatic steatosis were put on a diet and exercise program and later reevaluated.

Donor and Recipient Profiles

A total of 266 living donors with complete pretransplant CT data and histological assessment of intraoperative "time 0" liver biopsy was included in this study. There were 137 male and 129 female donors. Donor age, body weight, and BMI were 19–66 (median 38) years, 39–108 (median 61.3) kg, and 17.4–34.3 (median 22.6) kg/m^2, respectively. Selected graft types were left lateral segment in 122 donors, left lobe in 62, and right lobe in 82. Graft-to-recipient weight ratios (GRWR) for each graft types were 2.60 (range: 0.89–6.87), 0.96 (range: 0.61–1.56), and 1.14 (range: 0.66–3.18), respectively. Age and body weight of the recipients were 0.3–68.9 (median 11.1) years and 4.3–108 (median 28) kg. Primary disease of the recipients consisted of cholestatic disease in 138 patients, liver cirrhosis in 42, fulminant hepatic failure in 23, liver tumor in 23, metabolic liver disease in 20, retransplant in 12, and others in 8.

Donor Biopsy and Histological Assessment

During donor surgery, after confirming that there was no abnormal finding in the peritoneal cavity on gross examination, the "time 0" wedge biopsy was taken from the liver. When graft livers were left lateral segment, left lobe, or right lobe, biopsy specimen was taken from segment III, segment IV, or segment V, respectively.

Histological grading of macrovesicular steatosis of "time 0" biopsies was performed by two independent pathologists (S.M., H.H). Macrovesicular steatosis was defined as hepatocytes containing one large vacuole of fat displacing the nucleus peripherally, and graded as none, mild (30%), moderate (30%–60%), and severe (60%) based on the percentage of hepatocytes containing cytoplasmic fat droplets, as previously reported (*15*).

Calculation of L/S Ratio

All CT examinations were performed with a CT-W3000 (Hitachi Medical Systems, Tokyo, Japan). Scanning parameters were 120 kV, 200 mA, collimation of 7 mm, and table speed of 10 mL/s with reconstruction increments of 7 mm.

In noncontrast-CT, attenuation of normal liver is greater than the spleen. It has been reported that when this is reversed with a difference in liver-spleen attenuation of greater than 10 Hounsfield units, the liver is suspected to be steatotic (*16*). Hepatic and splenic attenuation values were measured on noncontrast-CT scans by using 16 circular region-of-interest (ROI) cursors in the liver and four in the spleen. In the liver, four ROIs were located in each of the right anterior, right posterior, left medial, and left lateral segments. This method was originally developed by us to raise the validity of the result by means of reducing errors in measurement and disappearance of overlap in each segment. All measurements were manually obtained in regions of uniform parenchymal attenuation, with care being taken to avoid vessels, artifacts, and other areas that might have spuriously increased or decreased measurements. The four measurements in each segment of the liver and spleen were averaged.

In this study, the ratio of attenuation values in the liver to those in the spleen (L/S ratio) was evaluated for its efficacy as a marker for steatosis in the liver (Fig. 1). Calculation of L/S ratio was as follows:

$$\text{L/S ratio} = \frac{\text{Average attenuation value of liver (16 points)}}{\text{Average attenuation value of spleen (4 points)}}$$

Inter-segmental variation of L/S ratio was also analyzed.

Statistical Analysis

Values are shown as median and range. For statistical comparison, chi-squared test or Fisher's exact probability test for categorical data, Kruskal-Wallis test or Mann-Whitney test for continuous data, Friedman test or Wilcoxon signed-ranks test for L/S ratio data of hepatic segments, and Cox-Mantel test for Kaplan-Meier survival curve were used. *P* values of less than 0.05 were regarded as statistically significant. To compare the preoperative diagnostic accuracy of L/S ratio, BMI, gamma-glutamyl transpeptidase (GGTP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholinesterase (ChE), and total cholesterol (T-CHO) receiver operating characteristic (ROC) analysis was used with the "time 0" biopsy taken as the gold standard. The ROC curve can be drawn by plotting sensitivity (or "true-positive rate") on the

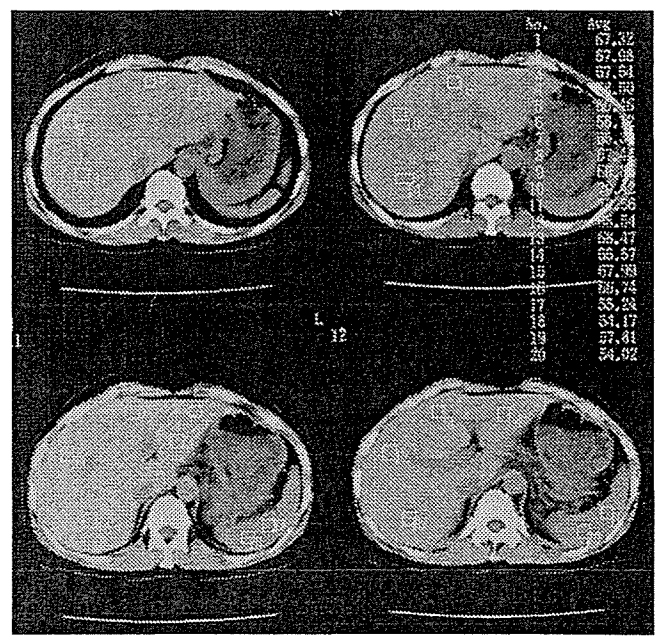

FIGURE 1. Calculation of liver-to-spleen CT attenuation values ratio. Hepatic and splenic attenuation values were measured on noncontrast-CT scans by using 16 circular region-of-interest (ROI) cursors in the liver and four in the spleen. In the liver, each four ROIs were measured at right anterior, right posterior, left medial, and left lateral segments. The size of one picture is 8 9 cm. Four sequential slices used for calculation of L/S ratio are demonstrated.

TABLE 1. Preoperative variables according to histological grades of macrovesicular steatosis

	Grade of macrovesicular steatosis (266)				
	None (198)	Mild (50)	Moderate (15)	Severe (3)	*P* values
Preoperative variables					
Donor age (yr)	37 (19–65)[b]	38 (21–61)[d]	48.5 (36–66)[b,d]	38 (30–47)	0.0127
BMI (kg/m^2)	21.9 (17.4–34.3)[a,b,c]	24.3 (18.0–31.6)[a,d]	26.5 (19.4–33.8)[b,d]	25.6 (24.1–26.8)[c]	0.0001
AST (IU/L)	17 (9–41)[a,b]	20 (11–87)[a]	23 (12–32)[b]	22 (11–25)	0.0001
ALT (IU/L)	14 (4–123)[a,b,c]	25 (9–142)[a]	26 (15–55)[b]	33 (20–47)[c]	0.0001
GGTP (IU/L)	16 (7–113)[a,b,c]	29 (10–90)[a]	27 (11–146)[b,e]	47 (30–87)[c,e]	0.0001
ChE (IU/L)	296 (168–508)[a,b]	345 (237–482)[a]	362 (277–486)[b]	309 (265–517)	0.0006
T-CHO (mg/dL)	188 (120–314)[a,b,c]	202 (139–441)[a]	214 (166–251)[b]	237 (222–249)[c]	0.0013
L/S ratio	1.20 (1.00–1.46)[a,b,c]	1.12 (0.83–1.37)[a,d,f]	1.01 (0.74–1.21)[b,d]	0.90 (0.70–0.99)[c,f]	0.0001

BMI, body mass index; AST, aspartate aminotransferas; ALT, alanine aminotranseferase; ChE, cholinesterase GGTP, gamma-glutamyl transpeptidase; T-CHO, total cholesterol; L/S ratio, liver-to-spleen CT attenuation values ratio.

[a]*P* 0.05 none vs. mild; [b]*P* 0.05 none vs. moderate; [c]*P* 0.05 none vs. severe; [d]*P* 0.05 mild vs. moderate; [e]*P* 0.05 moderate vs. severe; [f]*P* 0.01 mild vs. severe.

vertical (Y) axis and specificity (or "false-positive rate") on the horizontal (X) axis with a given cut-off point and changing the cut-off points from more stringent to less stringent. Because the accuracy of a test depends on its sensitivity and specificity, ROC curves of tests with higher discriminating ability are closer to the upper left corner than curves of those with lower ability (*17, 18*). Area under the ROC curve (AUC) can be calculated using the trapezoidal method (*17*). AUC represents the probability of correctly ranking a randomly chosen pair of persons with and without the disorder. For comparison of two AUC's, the nonparametric method developed by Hanley and McNeil (*17, 19*) was employed.

RESULTS

Graft Steatosis and L/S Ratio

The grade of macrovesicular steatosis as evaluated in the "time 0" biopsy specimens was none in 198 livers (74.4%), mild in 50 (18.8%), moderate in 15 (5.7%), and severe in 3 (1.1%) (Table 1). The median L/S ratio for livers of each histological grade was 1.20 (range: 1.00–1.46), 1.12 (0.83–1.37), 1.01 (0.74–1.21), and 0.90 (0.70–1.21), respectively. The differences among the four groups were statistically significant (Table 1). There were also significant correlations between steatosis grade in "time 0" biopsy specimens and increases in BMI or other blood chemistry results.

An intersegmental variation of L/S ratio was analyzed in the four segments (left lateral, left medial, right anterior, and right posterior segments) in patients with more than moderate grade steatosis (n 18). The L/S ratios in the left lateral, left medial, right anterior, and right posterior were 0.985, 0.985, 0.89, and 0.945, respectively. Although no statistically significant differences were observed among the four segments, L/S ratio tended to be higher in the left lateral segment than in the right anterior or posterior segments.

ROC Analysis

To compare the abilities of L/S ratio and other preoperative variables to discriminate between none to mild and moderate to severe steatosis, the ROC curves of these tests were determined (Fig. 2). The ROC curve of the L/S ratio was located closer to the upper left corner than that of any other preoperative variables (BMI, GGTP, ALT, AST, ChE, and T-CHO). For statistical comparison, Z statistics for the difference in areas under the ROC curves between L/S ratio and each of the other conventional variables are shown in Table 2. The AUC of L/S ratio was larger than that of any other variables, and the differences were significant, except for comparisons with BMI and ALT (Table 2).

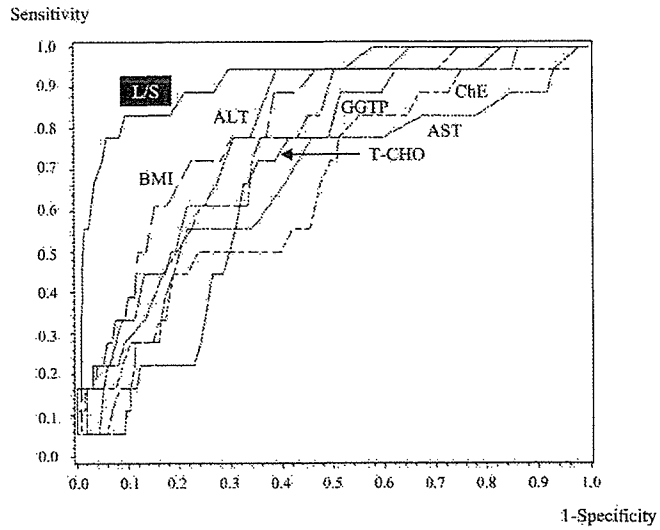

FIGURE 2. ROC curves were determined for L/S ratio, BMI, GGTP, ALT, AST, ChE, and T-CHO, all of which were measured preoperatively in 266 cases of LDLT.

Graft Outcome

Postoperative peak AST and ALT levels in both donors and recipients were higher in patients with moderate to severe macrovesicular steatosis. AST levels in donors with none to mild steatosis and in those with moderate to severe steatosis were 300 IU/L and 362 IU/L (*P* 0.05), respectively. Similarly, ALT levels in the respective donors were 270 IU/L and 388 IU/L (*P* 0.05). Moreover, the respective levels in recipients

TABLE 2. Statistical comparison of areas under the ROC curves between L/S ratio and preoperative variables

	Z statistics vs. L/S ratio	(*P* value)
BMI	1.61206	0.10695
GGTP	3.00589	0.00265
ALT	1.53605	0.12453
AST	2.74714	0.00601
CHE	3.37740	0.00073
T-CHO	2.94694	0.00321

were 295 IU/L and 417 IU/L and 317 IU/L and 418 IU/L, with no statistical differences being observed. However, the 5-year graft survival rates for grafts with none to mild steatosis and those with moderate to severe steatosis were 74.1% vs. 71.8%, but this difference was not significant. PNF was not seen in any of this series.

DISCUSSION

New insights into the mechanisms of failure of fatty livers should result in new prophylactic and therapeutic approaches (*20*). Livers with significant steatosis may increase the severity of ischemia-reperfusion injury and the incidence of graft PNF. Zamboni et al. (*21*) reported that macrovesicular steatosis involving 25% or more of the hepatocytes in the donor liver was significantly associated with shorter post-transplant survival and with a higher number of delayed graft failures. Worldwide, severely steatotic grafts (60%) are routinely discarded for CLT. On the other hand, use of graft liver with microsteatosis did not influence either short- or medium-term survival (*2*, *22*). In the case of LDLT, due to the limited selection of donors, grafts with moderate to severe grade steatosis have been sometimes used with fully informed consent. Probably due to the minimized cold ischemic time in part, PNF has not been observed in our series (cold ischemic time: 2 hr in this series). However, the risk of using grafts with severe steatosis has also been clearly identified in LDLT (*7*)

Although liver needle biopsy may be required for definitive preoperative diagnosis of hepatic steatosis, it is not a universally safe procedure and should not be routinely applied to all living donor candidates. To minimize the risks of liver needle biopsy, noninvasive diagnostic methods using clinical, imaging, and/or biochemical parameters have been investigated (*23*, *24*). In a recent study on living liver donors, Mary et al. (*8*) reported that BMI was a reliable predictor of hepatic steatosis with a positive correlation between increasing BMI and steatosis grade on biopsy. It was also suggested that liver biopsy could be avoided in subjects with normal BMI, but that living donors with high BMI should undergo liver biopsy because biochemical and imaging data are not reliable enough to accurately diagnose the degree of steatosis (*8*).

In the present study, ROC analysis was used to compare the diagnostic ability of L/S ratio to predict the grade of hepatic steatosis with that of other preoperative variables. Because the ROC curve of L/S ratio is closer to the upper left corner of the graph than that of other variables, the sensitivity and specificity of L/S ratio can be considered higher when compared with these variables (BMI, GGTP, ALT, AST, ChE, and T-CHO). The ROC curve is a graph of sensitivity versus specificity, both of which are independent of disorder prevalence, and analysis does not depend on the prevalence of disorder in the actual population to which the preoperative variable may be applied (*17*). Moreover, statistical analysis of the differences in AUCs reveals that L/S ratio could predict 30% hepatic steatosis more accurately than any other variable, although the differences were not significant in comparison with BMI or ALT.

If a liver with less than 30% steatosis is thought to be appropriate for a living donor, the mean SD of the L/S ratio in donors with none to mild steatosis was 1.184 0.091. With regard to discriminating between none to mild and moderate to severe steatosis by L/S ratio, when the cut-off level was set at 1.1, the sensitivity and specificity were 0.833 and 0.815, respectively (Table 3), and the ROC curve closely approached the upper left corner. With regard to balance between sensitivity and specificity, the optimal level of L/S ratio to predict 30% hepatic steatosis would be 1.1.

From the results of intersegmental variation of L/S ratio, it is likely that fat deposition is heterogeneous throughout the liver. Because a single biopsy specimen shows the grade of hepatic steatosis only at the area where it was taken, multiple needle biopsies would be necessary to accurately evaluate steatotic changes in the whole liver. On the other hand, evaluation of hepatic steatosis using CT attenuation values enables the assessment of fatty changes in each part of the liver. To simultaneously express a representative value of fatty changes of the whole liver as well as to estimate the risks of both the graft and the remnant liver, the averaged value was employed to determine L/S ratio in the present study.

The present study suggests that L/S ratio on noncontrast-CT can be clinically used as a noninvasive method to correctly evaluate hepatic steatosis. This method is actually feasible because CT examination has been routinely done in donor preoperative evaluation for the assessment of liver anatomy and graft size and the calculation of L/S ratio is not time consuming. By employing this modality, preoperative liver needle biopsy could be omitted for most donors at our institution. However, when hepatic steatosis of more than moderate grade indicated by the L/S ratio does not show any significant improvement regardless of adequate diet and exercise treatment, or is accompanied by other complications including diabetes mellitus and/or hyperlipidemia, liver biopsy is performed to exclude disorders such as nonalcoholic steatohepatitis.

TABLE 3. Assessment for cut-off point of L/S ratio more than 30% steatosis in time zero biopsy according to ROC analysis

Cut-off point of L/S ratio (≥30%)	Sensitivity	Specificity	Diagnostic accuracy
1.2	0.944	0.448	0.481
1.1	0.833	0.815	0.816
1.0	0.556	0.984	0.955
0.9	0.222	0.992	0.940
0.8	0.111	1.000	0.940

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ELSEVIER

S100 Protein: The Preoperative New Clinical Indicator of Brain Damage in Patients With Fulminant Hepatic Failure

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ABSTRACT

The aim of this study was to clarify the role of serum S100 on the accurate assessment of reversibility of brain damage after fulminant hepatic failure (FHF). Among the 13 patients with FHF enrolled in this study, 12 underwent living donor liver transplantation; one patient could not the procedure because of volvulus of the sigmoid colon.

Serum S100 was serially measured using a chemiluminescent immunoassay. Preoperative serum S100 in patients with diffuse brain edema was significantly higher than that in patients with localized brain edema (P 0.05). Patients with preoperative brain death showed serum S100 levels over 7.0 g/L.

Serum S100 levels correlated with the degree of brain edema of FHF. It has the potential to be a new clinical, noninvasive indicator of brain damage due to FHF.

FULMINANT hepatic failure (FHF), one of the most severe types of liver damage, may lead to severe hepatic encephalopathy and brain edema. In the most severe cases, patients are unable to undergo liver transplantation; irreversible brain damage leads to brain death. Despite advances in radiologic imaging such as computed tomography (CT) or magnetic resonance imaging (MRI), the preoperative diagnosis of irreversible brain damage caused by brain edema is difficult. The operability of FHF is decided based on the intracranial pressure (ICP), but this assessment is invasive, as it involves coagulopathy.[1] Therefore, a noninvasive and accurate assessment of the reversibility of the brain damage is required.

S100 protein is a dimeric acidic calcium-binding intracellular and extracellular protein found in the brain. It has a molecular weight of approximately 21 kDa. The three isometric subunits are (S100), (S100), and (S100 0). Because the subunit is present in a high concentrations in glial (astrocyte) and Schwan cells, measurement the subunit is highly brain specific. In this study, we investigated the subunit, which is eliminated or metabolized by the kidney, with a biological half-life of approximately 2 hours.[2] Recently, an increased subunit has been reported after the destruction of the microcircu-

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Table 1. Preoperative Neurologic Data and Serum S100 Protein Level

Case	Age	Gender	Type*	LDLT	Neurologic prognosis (complication)	Grade of encephalopathy	EEG	Brain edema on CT	S100 (g/L)	CHDF for renal failure
1	45	M	Subacute	Yes	None	II	Low voltage	None	0.03	( )
2	34	M	Subacute	Yes	None	II	Low voltage	None	0.05	( )
3	56	M	Acute	Yes	None	III	Slow activity	None	0.05	( )
4	44	F	Acute	Yes	None	III	Low voltage	None	0.12	( )
5	42	F	Subacute	Yes	None	IV	Low voltage Slow activity	Localized	0.03	( )
6	31	F	Acute	Yes	None	IV	Slow activity	Diffuse	0.69	( )
7	39	F	Subacute	Yes	None	IV	ND	Localized	0.29	( )
8	59	F	Acute	Yes	None	IV	Slow activity	Diffuse	0.21	( )
9	26	F	Subacute	Yes	None	IV	Flat line	Diffuse	0.65	( )
10	15	M	Subacute	Yes	Transient hemiparesis	IV	Slow activity	Localized	0.05	( )
11	0.3	M	Acute	Yes	Brain atrophy	IV	Low voltage	Diffuse	0.17	( )
12	23	F	Acute	Yes	None	IV	Slow activity	Localized	0.05	( )
13	44	F	Subacute	No	Preoperative brain death	IV	Flat line	Diffuse	7.23	( )

Abbreviations: LDLT, Living donor liver transplantation; EEG, electroencephalogram; CHDF, continuous hemodiafiltration.
*The type of fulminant hepatic failure.

lation as in a stroke, subarachnoid hemorrhage, head injury, or coronary artery bypass.[2–5] The aim of this study was to investigate the relationship between the severity of preoperative hepatic encephalopathy or brain edema of FHF and the level of serum S100 protein.

PATIENTS AND METHODS

Patients

Among 13 patients with FHF enrolled in this study 12 underwent living donor liver transplantation. One patient could not undergo transplantation because of sigmoid colon volvulus (Table 1).

Neurologic Assessment

The preoperative neurologic assessment included (1) hepatic coma scale (I to IVb), (2) electroencephalogram (EEG), and (3) CT.

Serum S100 Protein Analysis

Peripheral blood samples of S100 protein were obtained from patients just before plasmapheresis to exclude the influence of renal dysfunction. Also samples were obtained every 3 hours from admission to death from the patient who could not undergo LDLT. Clotted blood was centrifuged within 60 minutes (1000 G/10 minutes); the serum was stored at 80°C for subsequent analysis. The brain-specific glial S100 was analyzed in the serum using a chemiluminescence immunoassay with monoclonal antibodies directed against the human S100 protein (8 B10, 6G1). Briefly, 96-well PVL-round bottom microtiter plates were coated with 0.1 mL of clone 8B10 (2 g/mL PBS) at room temperature (RT) for 1 hour. Nonspecific binding sites were blocked with 0.2 mL of 1% BSA-PBS at RT for more than 1 hour. Plates were washed with PBS/tween-20 (PBST). Samples diluted with 1% BSA/PBST were incubated for 1 hour at RT. After washing, they were incubated (RT/1 hour) with 0.1 mL of POD-labeled 6G1 (diluted with 1%BSA/PBST-2 mmole $CaCl_2$). After washing, enzyme activity was assessed with 0.1 mL of 3,3′, 5, 5′ tetramethylbenzidine; absorbance was read at 450/650 nm. The detection limit of this assay was 0.01 g/L.

In this study, we investigated (1) whether serum S100 protein correlates with the degree of hepatic encephalopathy or brain damage during FHF before living donor liver transplantation, (2) the time course of serum S100 protein in the perioperative period, and (3) whether this marker has a potential to be a new clinical indicator of brain death in FHF with a case report.

RESULTS

All cases of stage II and III encephalopathy did not show brain edema on CT. On the other hand, all cases of stage IV encephalopathy indicated a diffuse or local brain edema on CT.

Serum S100 protein in patients with diffuse brain edema was significantly higher than in patients with localized brain edema (Fig 1A). Preoperative serum S100 protein levels in patients with diffuse brain edema (0.48 0.23 g/L) were significantly higher than that in patients with no edema or local brain edema (0.096 0.08 g/L) (*P* .014). The indicators of liver function, such as serum ammonia or international normalized ratio (INR) levels showed no correlation with serum S100 protein levels. Patient (Table 1) was able to recover despite a flat EEG before the transplant. This 26-year-old man, who had been diagnosed with acute FHF of unknown etiology, progressed into a deep coma unresponsive to the pain stimuli. His preoperative brain CT showed diffuse brain edema. The EEG was near flat without any change after painful stimuli, similar to that seen in brain death. At that point, his serum S100 protein was 0.65 g/L. He recovered consciousness without exhibiting neurologic complications after liver transplantation.

On the other hand, among the 12 patients who could undergo LDLT, the peak perioperative S100 protein level occurred immediately after the operation, (mean level 0.49 g/L; Fig 1B). These results suggest that serum S100 protein levels correlate with the degree of brain damage in FHF. With regard to these 12 patients, the reversible range of brain damage is under 0.78 g/L (the peak of serum S100 protein level immediately after the operation).

Figure 2 shows the time course of a case diagnosed with brain death preoperatively. The patient could not undergo

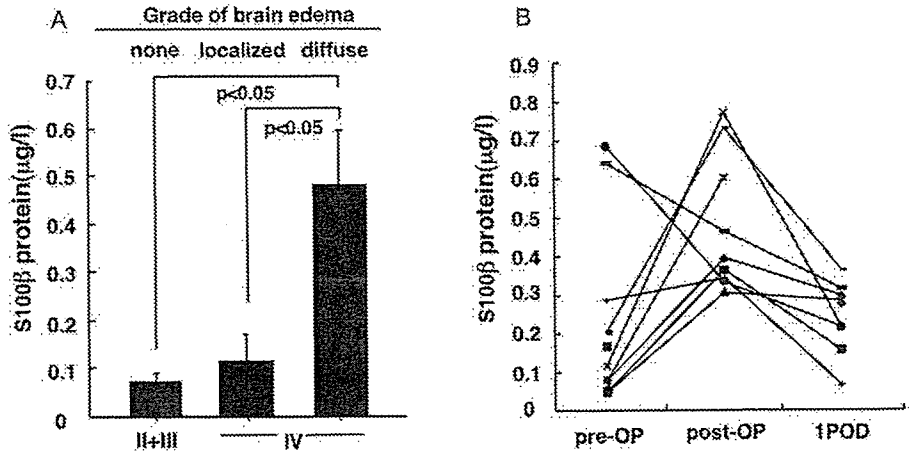

Fig 1. The relationship between the degree of neurologic damage and serum S100 protein level in 12 patients that underwent LDLT. **A.** Preoperative serum S100 protein level in patients with diffuse brain edema (0.48 0.23 g/L) was significantly higher than in patients with no edema or local brain edema (0.096 0.08 g/L) (*P* .014). Also the serum S100 protein level consistently increases with the severity of brain edema on CT (mean level; none: 0.075 g/L, localized: 0.117 g/L, diffuse: 0.48 g/L). **B.** Perioperative serum S100 protein level. The peak of S100 protein occurred immediately after the operation (0.78 g/L), and the mean level 0.49 g/L was within the normal range.

LDLT due to sigmoid colon volvulus. This 44-year-old woman suffered from FHF of unknown etiology. Twelve hours after the operation for volvulus, she was found to be unresponsive to any stimuli, as demonstrated by EEG and brain CT (Fig 2). The EEG showed a flat line and the brain CT showed severe diffuse edema. These tests strongly suggested brain death, but were not sufficient for such a diagnosis. At this point, her serum S100 protein level was 1.09 g/L, a level that continued to increase. By the time brain death was declared, it had reached 7.0 g/L.

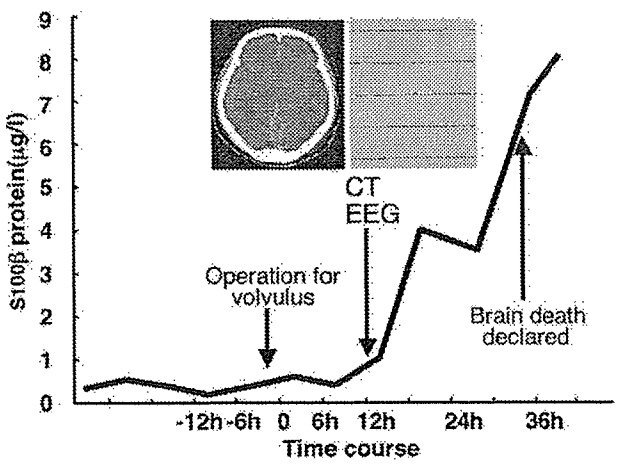

Fig 2. Time course of a case diagnosed with brain death preoperatively where the patient could not undergo LDLT. She was a 44-year-old woman suffering from FHF with unknown etiology and developed volvulus of the sigmoid colon. Twelve hours after the operation for volvulus, she was found to be unresponsive to any stimuli, which was shown on the EEG and brain CT. These tests strongly suggested brain death, but were not sufficient for such a diagnosis. At this point, her serum S100 protein level was low, but continued to increase. When brain death was declared, the serum S100 protein level had reached 7.0 g/L.

DISCUSSION

Despite advances in radiologic imaging such as CT or MRI, it is still difficult to establish a diagnosis of irreversible brain damage caused by brain edema in patients with severe liver damage. Generally, the operability of FHF is based on the ICP, but this assessment is invasive and it involves a coagulopathy.[1] So a noninvasive, accurate assessment of the reversibility of brain damage is required. Although EEG is an excellent research tool, it is still undergoing validation. In FHF, we sometimes encounter cases where the EEG is able to return to normal after liver transplantation, despite having flat lined. Also at this point in time there is no report addressing the relationship between CT or MRI and the grade of brain damage in FHF.

In a recent study, the level of a marker of astroglial dysfunction—S100 protein—was reported in neurologic diseases, such as stroke, subarachinoid hemorrage, head injury, and coronary artery bypass.[2–5] Ytrebo et al[6] described elevated serum S100 due to acute hepatic encephalopathy in pigs. Because astrocytes are the primary site of edema formation in encephalopathy with liver dysfunction, we hypothesized that S100 might be an early marker of the severity of brain damage in patients with FHF. In the previous study, S100 protein levels in excess of 0.5 mg/L were considered pathologic.[7] Our results indicate that the preoperative serum S100 protein level was not more than 0.69 g/L among patients who recovered consciousness without neurologic complications after LDLT.

S100 protein is metabolized by the kidney; its biological half-life is approximately 2 hours. Consequently, elevated

S100 protein levels in patients with FHF may result from decreased renal elimination. However, in this study, every patient underwent continuous hemodiafiltration (CHDF) to remove cytokines or low-molecular-weight toxins. Their preoperative mean creatinine value was 0.96 mg/dL, thereby excluding an influence of kidney failure. Furthermore, serum S100 protein is eliminated by plasmapheresis (PE).[8] So we sampled blood just before PE to exclude this influence.

Serum S100 protein levels showed a correlation with the degree of brain damage, but not with serum ammonia or INR levels. This result suggested that S100 protein can simply assess brain damage without an influence of liver function.

There is only one report concerning the relationship between brain damage and S100 protein in FHF. Gitte et al[8] reported no significant difference in S100 protein levels between patients who survived without liver transplantation compared with those who subsequently died of cerebral herniation in FHF. They diagnosed cerebral herniation only by physical examination without any images, it was too late to determine operability. We required an indicator of the diagnosis—an EEG, CT or MRI.

Wiltrang et al[9] reported that serum S100 was specifically elevated in hepatic encephalopathy associated with portal-systemic stent-shunt in patients with liver cirrhosis. In the present study, we reported that S100 protein correlates with the degree of brain damage (grade of brain edema) and the CT appearance in FHF before LDLT (Fig 1). Furthermore, we reported that this marker was significantly elevated before a diagnosis of brain death by CT or EEG with a case report (Fig 2). In conclusion, these results suggest that serum S100 protein has the potential to be a new clinical indicator of brain damage in FHF.

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肝移植

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abstract

肝細胞癌に対する肝移植は，Bismuth，Mazzaferroらが適応の判定を厳密に行えば良好な成績が得られることを報告して以来，再び盛んに行われている．いわゆるミラノ基準を満たせば再発率は非常に低いが，肝外転移・脈管浸潤を認めなければミラノ基準をはずれても60%を超える症例で再発を認めない．ミラノ基準外症例を生体肝移植の適応外とする場合，治癒の可能性にかける患者とドナーの権利を奪うことの是非は問われるべきである．

肝移植の適応は，癌の進展度と肝予備能の両面から判定される．近年のアブレーション治療の急速な発達によって治療法選択は以前より複雑化している．正確な予後判定と肝移植を含めた治療法選択のためのスコアリングシステムが各国から次々と報告されてきた．肝細胞癌では再発を繰り返し治療歴が長期にわたることが多いが，いつ肝移植を決断するかの問いにこたえることはいまだに難しい．

I はじめに

2004年1月から成人の肝硬変，劇症肝炎に対する生体肝移植が保険適用となった．同時にいわゆるミラノ基準に合致する肝細胞癌（HCC）に対しても保険適用が認められ，これまで経済的な理由で肝移植をあきらめざるをえなかった多くの患者にとって朗報となった．一方保険診療と認められたことで，HCC治療の選択肢のなかのひとつとして他の治療法と同列線上でそのメリット・デメリットを患者と家族に的確に提示する必要が生じてきた．

一方，生体肝移植は，ドナーに対する身体的・精神的・経済的なリスクのうえに成り立つという特殊な本質をもっている．肝切除，ラジオ波焼灼術（RFA），経皮的エタノール注入療法（PEIT），肝動脈塞栓療法（TAE）と治療オプションの幅が広がっている現在，この特殊な治療法を含めた選択肢のなかでどれを最適と判断するかは非常に難しい問題である．脳死肝移植を念頭に，長くこの問題が論じられてきた欧米でも，最近では生体肝移植の施行例が増加してきており問題は複雑化している．

本稿では，HCCに対する生体肝移植のこれまでの経験を踏まえて，現状でこの問題にどうこたえるかについて論じる．

II 肝癌に対する肝移植の適応

肝移植の適応となるのは，肝臓を入れ替えることで完治が期待される肝臓に限局している癌である．転移性肝癌では血行性に多臓器へすでに微小転移があると考えられ，予後が改善されないために適応と

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はならない．例外は一部の内分泌腫瘍の肝転移で，原発巣がコントロールされており肝外への転移がなく長期に安定していれば肝移植の適応となりうるものがある．肝原発である癌でも胆管癌は移植後の再発率がきわめて高いことが知られており[1),2)]，通常は肝芽腫に加えてHCCだけが肝移植の適応となっている．

III 脳死肝移植と生体肝移植

脳死肝移植では，絶対的にグラフトが不足しているなかで，waiting list上の多くの患者のうち，誰に移植するかを決めなければいけない．このため，脳死グラフトには共有財産的な性格が生じ，患者の病状の緊急性ばかりでなく，肝移植によりどのくらい予後が見こめるかについても考慮する必要がある[1)]．

これに対し，生体肝移植ではドナーからレシピエントへのあくまで個人的なプレゼントであり，患者とドナーの移植に対する希望の強さが大きな意味をもっている．また一方では，予後が十分期待できない病状ではドナーにリスクを負わせることの正当性を問われることになり，患者および家族の意志決定に際してできる限り正確な予後予測の情報を与える義務がある．

IV HCCに対する肝移植適応の変遷

肝原発の癌として最も多くを占めるHCCは，初期には遠隔転移を起こしにくく，一方肝内においてはmulticentricに発生する[3)]．肝臓を入れ替える肝移植がHCCに対する最も強力な治療法であるのは[4)~8)]，腫瘍のこの病理学的性格によっている．しかしながら1970年代から80年代にかけて行われたHCCに対する肝移植の成績は惨憺たるものであった．これは移植後の再発率が高く，適応の判定が適当ではなかったことに原因がある．この時期の成績の分析で，血管侵襲リンパ節転移，肝外進展のある症例では再発率が高いと報告されているが[9),10)]，現在，ミラノ基準よりも広い適応基準で移植を行っている施設においても，これらの症例は適応から除外しているのが通例である．

その後，初期の悪い成績を受けて，HCC治療としての肝移植は熱を失い1980年代，一般にはほとんど行われなくなった．ところが，近年，いくつかの施設から，腫瘍の進展度によって適応を厳密に判定すれば，良好な成績が得られることが報告されるようになり[10),11)]，HCC治療としての肝移植が再び注目を集めるようになった．Bismuthらは「3cm 2個までの病変では生存率・無再発率とも肝切除より肝移植の成績が優れている」と報告し[12)]，Mazzaferroらは「3cm 3個まで，単発5cmまでの病変では，移植後再発が非腫瘍例と差がない」と報告した[13)]．

V ミラノ基準

Mazzaferroらの報告はミラノ基準とよばれ，脳死肝移植でのグラフト不足を背景として，その後多くの移植施設で適応判定のガイドラインとして採用されてきた．また本邦における2004年1月からの保険適用の基準にも採用された．しかしながら，この基準を満たすとして移植を受けた症例のなかにも再発をきたすものがあり，反対にミラノ基準を外れても再発をきたさない症例も多い．その原因として術前の画像診断と摘出肝の組織学的所見のギャップが無視できない．近年，画像診断の精度が急速に向上し，この問題は以前よりも小さいものになってきているが，今後も常に組織所見の検討によるフィードバックが必要である．また，絶対的グラフト不足によって優先順位をつけざるをえない脳死肝移植では，低い成功率しか見こめない患者は移植を受けることが難しい．これに対して，生体肝移植においてグラフトは個人的なプレゼントであり，もしもドナーとレシピエントがより低い成功率にも望みをかけたいとしている場合には，同一の論理では適応を判定できない．

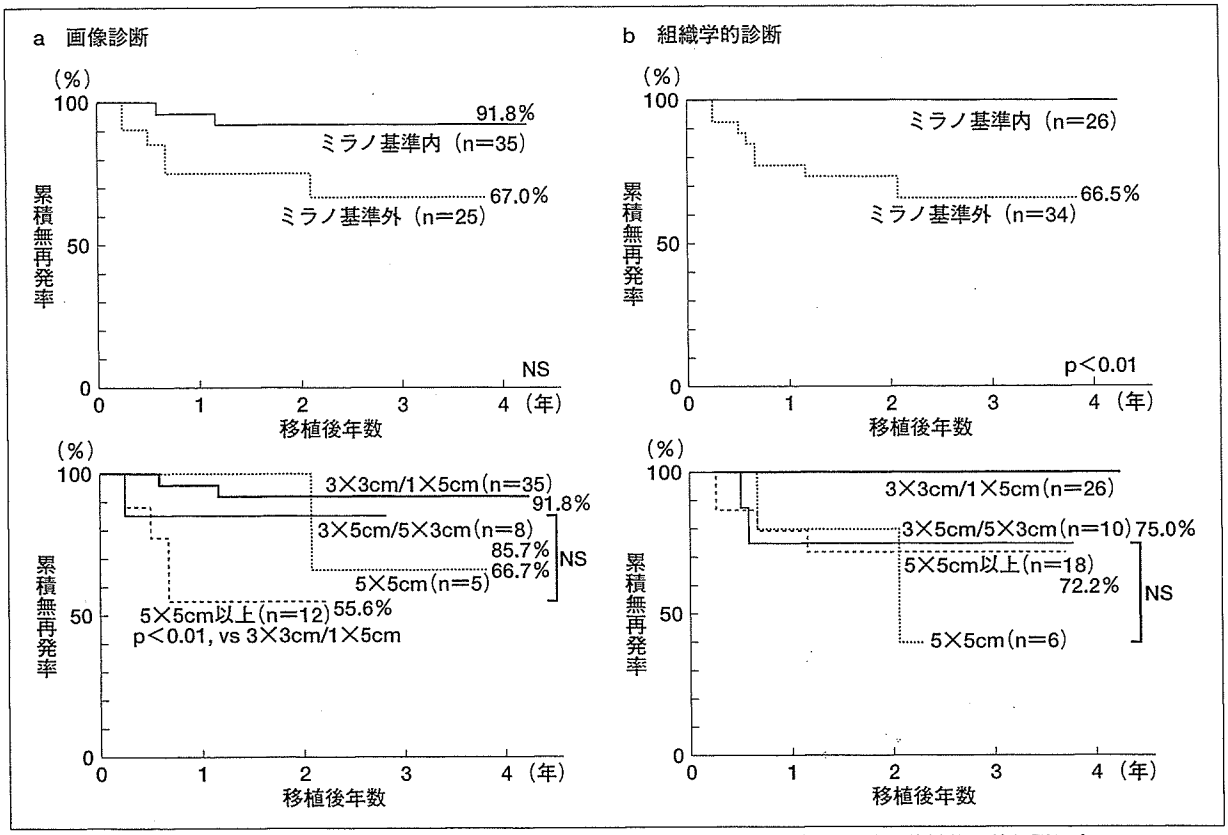

図1 成人HCC症例（n=60）におけるミラノ基準分類（上），腫瘍個数・最大径（下）と生体肝移植後累積無再発率

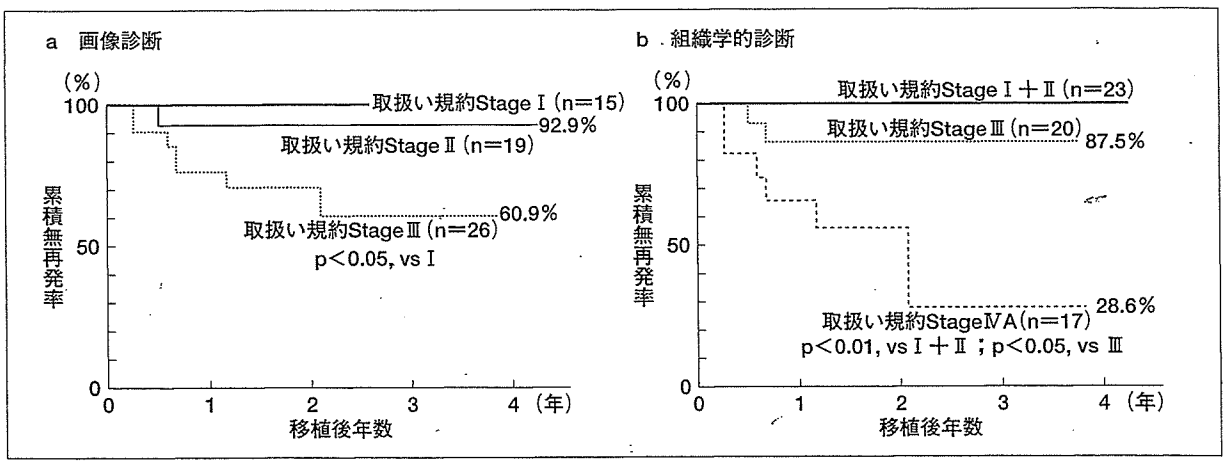

図2 成人HCC症例（n=60）における原発性肝癌取扱い規約分類と生体肝移植後累積無再発率

Ⅵ 生体肝移植のHCCに対する適応

これまでの成績から学ぶもの[14]

肝移植後の再発に影響する因子として，腫瘍個数，分布，最大径，脈管浸潤，リンパ節転移，分化度などが報告されてきた．図1に，京都大学における初期HCC症例60例に対する生体肝移植の再発成績を示す．entry criteriaは移植前に脈管浸潤が証明されなかった肝内限局の病変である．腫瘍の個数，サイズには制限を設けていない．ミラノ基準外の症例で

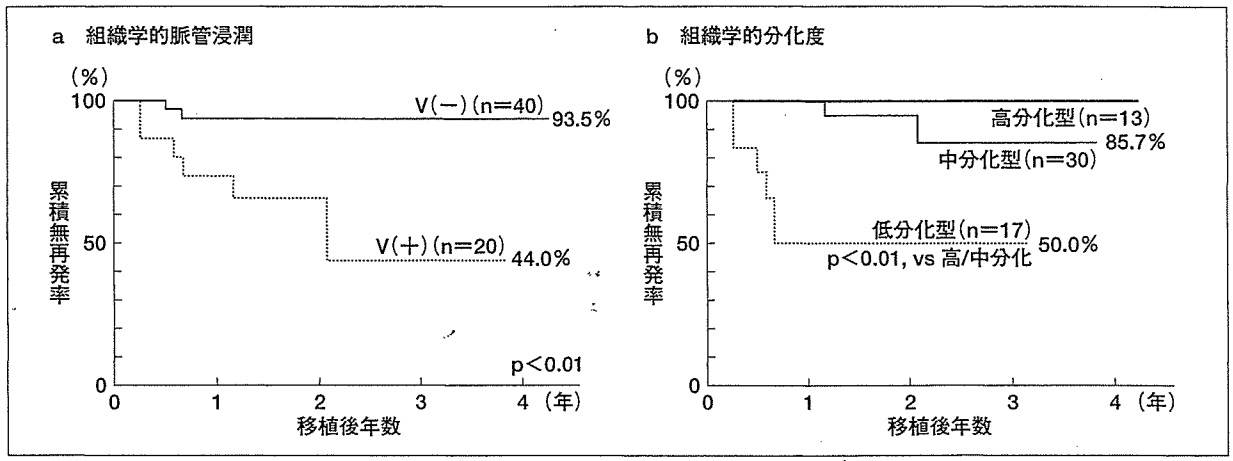

図3 成人HCC症例（n=60）における組織学的脈管浸潤・分化度と生体肝移植後累積無再発率

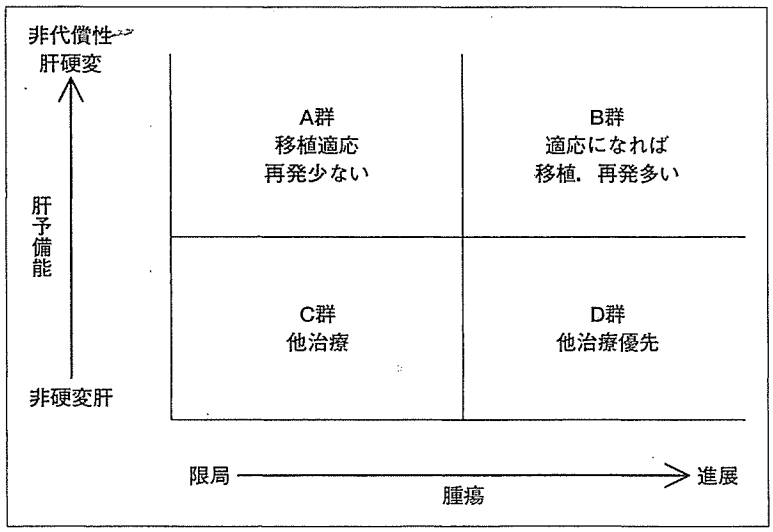

図4
HCCに対する肝移植適応の概念

は再発率が高い傾向が明らかである．組織学的診断では有意差をもって再発率が高いが，なお4年で66%の症例が無再発である．

図2は，原発性肝癌取扱い規約による分類での再発成績である．**図2a**は術前画像診断で脈管浸潤がないと判断された症例であるため最高でstage Ⅲである．組織学的検索によって微小な脈管浸潤（主としてVp）を認めたstage ⅣAでは再発率は70%と高い．術前画像診断ではstage Ⅲと診断された症例のなかに組織学的検索によってstage ⅣAと診断されるものが多く含まれており，組織診断上のstage Ⅲ症例では再発率は10%程度であるのに対して，術前画像診断でstage Ⅲと診断された症例の再発率は40%と高くなっている．画像診断が高度に発達してきた現在でも，術前の画像からVpを診断することは難しく，組織学的なstage分類と術前の画像診断によるstage分類とのギャップは埋めがたい．術前のstageによって予後予測を行い，適応を決定することの難しさがこの点にある．

図3aは，組織学的脈管浸潤の有無による再発率を示す．脈管浸潤を有する例は，組織学的に初めて診断される微少なものであるにもかかわらず高率に再発している．また，**図3b**からは，腫瘍の組織学的分化度が下がるほど高率に再発しており，組織学上の所見が再発率によく相関することがわかる．問題はこれらの因子を反映した術前stagingの確立が困難なことである．

	Okuda	CLIP	BCLC	French	CUPI	JIS
腫瘍因子	サイズ（画像占有面積）	個数，進展度 AFP	個数，進展度 Okuda	AFP Karnofsky index	TNM AFP	TNM
肝機能因子	Alb Bil 腹水	Child-Pugh 門脈血栓	Performance status Child-Pugh Okuda	Bil ALP 門脈血栓 Karnofsky index	Bil ALP 腹水 症状の有無	Child-Pugh

表1
HCCのスコアリングシステム

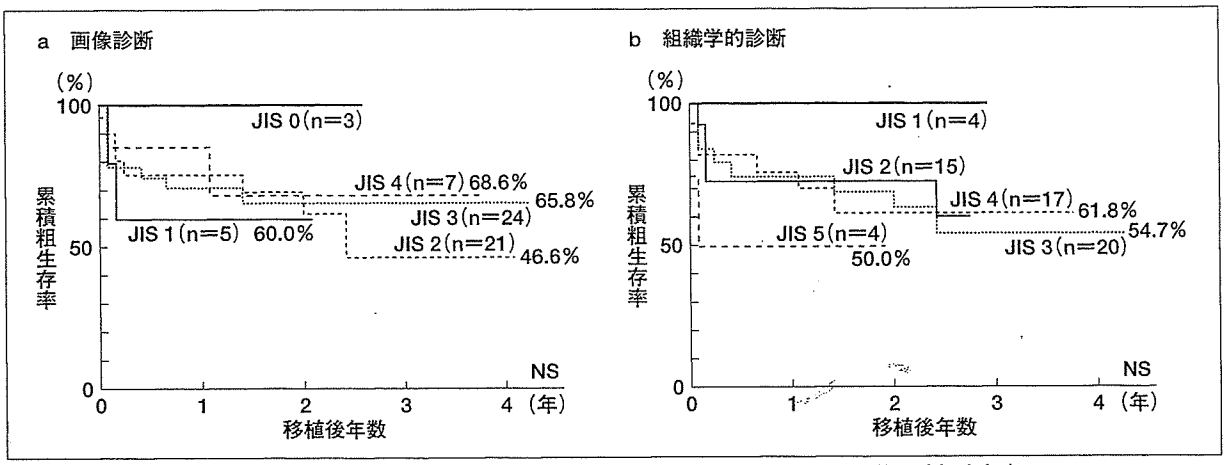

図5 成人HCC症例（n=60）におけるJapan Integrated Staging（JIS）スコアと生体肝移植後累積粗生存率

Ⅶ 他の治療法との選択

HCCの各症例で肝切除，RFAなど他の治療を行うか，肝移植を選択するかについてはいまだ議論が多い[15]．この適応判定に際しては腫瘍のstageだけでなく肝臓の予備能を含めて決定されなければならない[7]．図4はこの概念を整理したものである．進行した肝硬変で予備能がなく，他の治療ができないが，腫瘍のサイズ・個数が限局しているものは，肝移植によって根治が期待されよい適応である（A群）．より進んだstageの腫瘍に対しては，治療の及ぶ範囲も広くなり，予備能の低い肝臓では，移植以外の治療は困難になる（B群）．しかし腫瘍が進行していれば移植後の再発率は高くなり，高い再発率から移植の適応をはずれる症例も出てくる．一方，予備能が十分あり腫瘍が限局しているものでは，肝切除など移植以外の治療を行う（C群）．肝切除，肝移植いずれにも経験の多い施設から，肝硬変であれば肝切除に十分耐術できる肝予備能であっても長期予後の点から肝移植を優先するという結論も出されている[7, 16]．しかしながら，脳死肝移植においてはグラフト不足を，生体肝移植においてはドナーのリスクを考慮すれば，移植以外の治療で十分な効果が期待できる肝機能を有した症例に対しては，安易に肝移植を選択するわけにはいかないはずである[17]．非硬変肝を背景として発生したHCCで，腫瘍が両葉散布性に広がった症例に対して，肝機能の点からではなく腫瘍切除の根治性を期待して肝移植が行われることがある．しかし，こういった症例での移植後再発率は非常に高く，肝移植の適応とすべきではないとするのが一般的で[1, 7]，まずはTAE/経カテーテル的肝動脈注入療法（TAI）などを考慮すべきである（D群）．

肝移植を選択した場合，肝臓は入れ替わるのだから肝不全の程度は成績に影響がないというのは全くの誤解である．特に慢性の肝硬変をベースに急性増

悪をきたした症例（旧UNOS分類 status2A）では予後は悪く，脳死全肝移植のオプションをもつ欧米では，こうした成人症例を生体部分肝移植の適応外とする施設も多い．肝不全が進行することによる肝移植の成績悪化はHCCの移植適応を考える際にも忘れてはならない要素で，タイミングを逸しないことが重要である．

Ⅷ スコアリングシステム

HCC症例の肝移植適応を論ずる際には，腫瘍因子と肝機能因子の双方を考慮しなければならない．HCCの治療方針を決定するために，この2因子を含めたスコアリングシステムが使われてきた（**表1**）．最も早くに提唱されたものがOkuda分類である．その後，イタリア（Cancer of the Liver Italian Program：CLIP），スペイン（Barcerona-Clinic Liver Cancer：BCLC），フランス，中国（Chinese University Prognostic Index：CUPI）からそれぞれstage分類の報告があり，日本からは原発性肝癌取扱い規約とChild-Pugh分類を組み合わせたJapan Integrated Staging（JIS）が提唱されている（**図5**）．CLIPはOkuda分類よりも正確な予後予測を主張し，BCLCはstage分類に基づいた具体的な治療プランのアルゴリズムを示すなどの特徴がある．最近使用されることの多いCLIPに対して，JISは根治的治療法の対象になりやすい低いstageの患者の階層化・分類化がより正確であるとされている．

しかしながら，肝切除，RFA後の再発HCCに対していつ肝移植が適応になるのか，何度まで繰り返してRFA治療の適応とするのか，進行したHCCでは肝移植の前にTAEをしたほうがいいのか，など現実の肝癌治療で直面する多くの問題に十分こたえられるだけのスコアリングシステムはいまだに存在せず，個々の症例で微妙で困難な判断を迫られている．このような状況のなかで，アブレーション治療中にコントロールされていた病変が突然肝外転移や明らかな脈管浸潤をきたして生体肝移植の準備をしていた家族を失望させる，あるいはRFA穿刺経路に沿って播種していることが移植術中に発見されるなどの事例がある一方で，アブレーション治療などで十分コントロールできると思われる症例でも，家族の移植に対する過度の期待（“再発のない夢の治療”といった誤解）がドナーに対するリスクを軽視させ，他の治療オプションの提案に耳を貸さないといった問題も起こっている．

Ⅸ おわりに

腫瘍因子と肝機能因子を組み合わせたスコアの提唱によって，病状の進行度を階層化したなかでそれぞれの治療法の成績比較が可能になってきている．しかし，現実の治療の局面で遭遇するさまざまな問題，特に肝切除，RFA，TAE/TAI，PEITなどの治療を行っていく時間経過のなかで，いつ肝移植を考えるかとの問いには十分な回答を与えているとはいいがたい．現状では個々の症例で，その時々の治療選択肢に対するできる限り正確な情報を患者および家族に提供し，各時点で話し合っていくことが最も適切な対応と思われる．

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総　説

移植医療における深在性真菌症

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要　旨

臓器移植領域における深在性真菌症は，ほとんどが *Candida* と *Aspergillus* によるものであり，小腸・肝・膵・肺移植での頻度が高い．限られた情報ではあるが移植臓器別に危険因子が挙げられているが，これに基づいた抗真菌薬の予防投与や先制攻撃的使用についてはその効果について充分な証明のなされていないものも多い．術前状態や手術因子，免疫抑制因子も含めた移植領域の特性に基づいた症例の階層化を行い臨床的裏付けに基づいたテーラー・メードの指針に到達するためには，多くの試案と検証とを繰り返していく必要がある．

Key words: 臓器移植（solid organ transplantation），深在性真菌症（invasive mycosis），予防投与（prevention），先制攻撃的治療（preemptive treatment），階層化，(stratification)

はじめに

本邦の臓器移植医療は，腎臓移植が既に欧米に劣らぬ長い歴史をもつにも関わらず，近年の生体肝移植の普及といわゆる'脳死移植法'下の心臓移植や肺移植の開始に伴って，急速に一般医療の一部として認識されるようになってきた．深在性真菌症の発生頻度は，腎移植よりも肝移植や肺移植においてずっと高く，本邦においてもその診断と治療のガイドラインが求められ始めた．本稿では，第47回日本医真菌学会総会シンポジウムでの発表をもとに，第1版「深在性真菌症の診断・治療ガイドライン」をふまえて，欧米の状況を紹介しながら今後の方向性を考える一助としたい．

真菌感染制御からみた臓器移植領域の特性

感染症制御からみた移植領域の特性としては，1）臓器不全のために移植時には既に免疫不全状態が存在する，2）移植前の感染治療歴のために菌交代をきたしている場合が少なくない，3）手術侵襲と初期の不安定な移植臓器機能，さらに免疫抑制導入のために免疫不全が増強される，4）感染の初期兆候が抑制されるため，診断が遅れる場合がある，5）治療の際には免疫不全因子の改善が必要なことが多い，6）併用薬剤が多く，相互作用や毒性の増強に留意が必要である，などが挙げられる．一般に細菌・真菌感染の発生は術後の1～2か月間に集中するが，そのリスクは移植臓器，免疫抑制の程度，さらに外科的因子に左右され，状況によっては6か月程度までリスクがある．患者の"総合的免疫低下状態（net state of immune suppression)"と治療的侵襲，さらに体内・体外の環境因子を考慮して個々の症例のリスクを判定しなければならない．

臓器移植患者における真菌感染は，ほとんどが *Candida* と *Aspergillus* によるものであり，その全体の頻度は減少傾向にあるものの，重症化した場合の死亡率は依然高い[1]．また，侵襲性カンジダ症減少の一方で，アゾール系薬剤耐性菌の増加や，侵襲性アスペルギルス症の増加も認められている[2]．

移植臓器別にみた真菌感染とその危険因子

深在性真菌症の頻度は，腹部臓器では小腸・肝・膵移植で，胸部臓器では肺移植で高いとされるが，報告によって大きな差がある[3,4]．危険因子としては，高用量ステロイド，繰り返す拒絶治療，耐糖能障害，移植臓器機能低下，白血球減少などが挙げられている．心移植，続いて肺・肝移植においては *Aspergillus* の頻度も高い．

肝移植患者では侵襲性カンジダ症の頻度が高く，上記の危険因子に加え，抗生剤の多用，緊急／再移植，経腸管的胆道再建，サイトメガロウイルス感染，腎不全など多様な危険因子が挙げられている[3,4]．*Candida* の colonization は，特異性は高くないが，侵襲性カンジダ症のリスクのよい指標となる．外科的技術や移植のタイミングの改善，さらにステロイド使用の減少により，一般に真菌感染の頻度は減少しているが，高度肝・腎不全症例や大量ステロイド使用症例で院内環境が絡むと *Aspergillus* 感染も無視できない頻度になる[4]．侵襲性アスペルギルス症の発症時期は肝移植ではやや早く，播種化する頻度も高い．移植後に低下しない β-D-glucan 値は重症感染や予後のよい指標となる．

肺移植では気道の colonization が多く，特異性は高くないが気管気管支炎や侵襲性感染のリスクを反映する[4]．侵襲性アスペルギルス症のほとんどが *A. Fumigatus* に

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