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MAJOR PAPER

Validity and Reliability of Magnetic Resonance Elastography for Staging Hepatic Fibrosis in Patients with Chronic Hepatitis B

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Purpose: We evaluated the validity and reliability of magnetic resonance elastography (MRE) for staging hepatic fibrosis in patients with chronic hepatitis B.

Methods: The study included 73 patients with chronic hepatitis B and confirmed stages of pathological fibrosis. Two radiologists measured liver stiffness using MRE in all cases. We compared the area under the receiver operating characteristic (ROC) curve (Az) for distinguishing stages of fibrosis compared with MRE liver stiffness measurements and serum fibrosis markers. We used intraclass correlation coefficients to analyze interobserver agreement for measurements of liver stiffness and 2 one-sided t-tests to test the equivalence of the measurements by the 2 observers.

Results: ROC analyses revealed the significantly superior discrimination abilities of MRE for liver fibrosis staging (Az = 0.945 to 0.978 [Observer 1] and 0.936 to 0.967 [Observer 2]) to those of serum fibrosis markers (0.491 to 0.742) for both observers ($P < 0.0004$). The intraclass correlation coefficient between the 2 observers was excellent ($\rho = 0.971$), and the measurements of liver stiffness by the 2 observers were statistically equivalent within a 0.1-kPa difference ($P = 0.0157$)

Conclusion: MRE is a valid and reliable technique for discriminating the stage of hepatic fibrosis in patients with chronic hepatitis B.

Keywords: ***chronic hepatitis B, hepatic fibrosis, liver stiffness, magnetic resonance elastography, serum fibrosis marker***

Introduction

Accurate staging of hepatic fibrosis is important in the management of chronic liver disease because the stage of fibrosis is closely related to prognosis and risk of hepatocarcinogenesis.[1,2] The management of chronic hepatitis B (CHB) depends on the degree of fibrosis as well as preserved liver function and presence of hepatocellular carcinoma. Cirrhosis is believed to be irreversible, but increasing evidence indicates that mild fibrosis and cirrhosis in patients with CHB are reversible when properly treated.[3,4]

The staging of liver fibrosis commonly involves liver biopsy followed by histopathological assessment. However, biopsy can cause such complications as hemorrhage and infection, and its inherent drawbacks include sampling error, high interobserver variability, and low patient compliance.[5–7] Consequently, noninvasive methods have been developed for assessing hepatic fibrosis that include the assessment of several proposed serum fibrosis markers, including the ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT) (AAR),[6] the AST-to-platelet ratio index (APRI),[7]

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the fibrosis-4 (FIB-4) index,[8] and the fibrosis quotient (FibroQ).[9] Magnetic resonance elastography (MRE), a modified phase-contrast technique developed to characterize the elasticity of tissues, is a new technique employed for staging noninvasive liver fibrosis. Recent studies have indicated MRE as a promising, highly reproducible tool with advanced diagnostic capacity for the noninvasive staging of hepatic fibrosis.[10–14]

In general, different causes of liver disease produce dissimilar patterns of fibrosis that may affect the stiffness value.[15] For example, pericellular fibrosis is a characteristic feature of alcoholic hepatitis, whereas periportal degeneration and fibrosis appear to be more prominent in chronic hepatitis C (CHC).[16] It is believed that CHB has a tendency to involve more advanced focal necrosis and inflammatory cell infiltration than CHC. Unfortunately, the number of MRE studies is limited for groups with a single etiology, such as CHC,[13] CHB,[17,18] alcoholic hepatitis,[19] nonalcoholic steatohepatitis (NASH),[20,21] and Gaucher disease.[22] Accordingly, it appears that more evidence would have to be collected using subjects with single-etiology liver disease to establish the use of MRE in clinical settings.

One criticism raised for MRE is that inhomogeneity on a stiffness map might lead to varying measurements depending on the placement of the region of interest (ROI). To provide consistency in ROI measurements, a confidence map has been proposed that is based on the correlation coefficient of polynomial fits during application of an inversion algorithm.[23] However, such a map might exclude the best area for ROI measurement because the algorithm is performed without knowledge of the anatomy.[24] An alternative means to achieve consistent measurements is to follow predetermined rules using an MRE phase image as well as a stiffness map. On the MRE phase images, the presence of a parallel wave form without interference is a hallmark of well propagating elastic waves in the liver. Consequently, it would make sense to place ROIs on phase images in areas in which straight elastic waves are visualized. Although previous results indicated high repeatability of MRE,[11,25] little is know about interobserver agreement according to the placement of ROIs.

Hence, we evaluated the accuracy and reliability of MRE for staging liver fibrosis in patients with chronic hepatitis B by comparing the diagnostic ability between MRE and serum fibrosis markers, and we secondarily assessed agreement between 2 observers.

Materials and Methods

Patients

This retrospective study was performed in accordance with the principles outlined in the Declaration of Helsinki, and was approved by the relevant institutional review board. Between January 2010 and May 2014, 1516 consecutive patients underwent MRE for liver investigations. Patients were included in the study with type B chronic hepatitis, available MRE data, histopathological determination (METAVIR scoring system) of hepatic fibrosis stage available within 6 months of MRE, and laboratory test results available within one week of MRE. We excluded 3 patients because the associated gradient echo-based MRE sequences did not provide a measurable stiffness map due to severe iron deposits, 3 patients with insufficient amounts of liver tissue from tissue biopsy to assess the stage of fibrosis, 3 patients with both CHC and CHB ($n = 3$), and one patient with both CHB and alcoholic hepatitis. After applying the inclusion criteria, we enrolled 73 patients (57 men, 16 women; aged 39 to 82 years, mean age 62.8 ± 9.6 years) in the study (Fig. 1).

Liver specimens were obtained by liver biopsy in

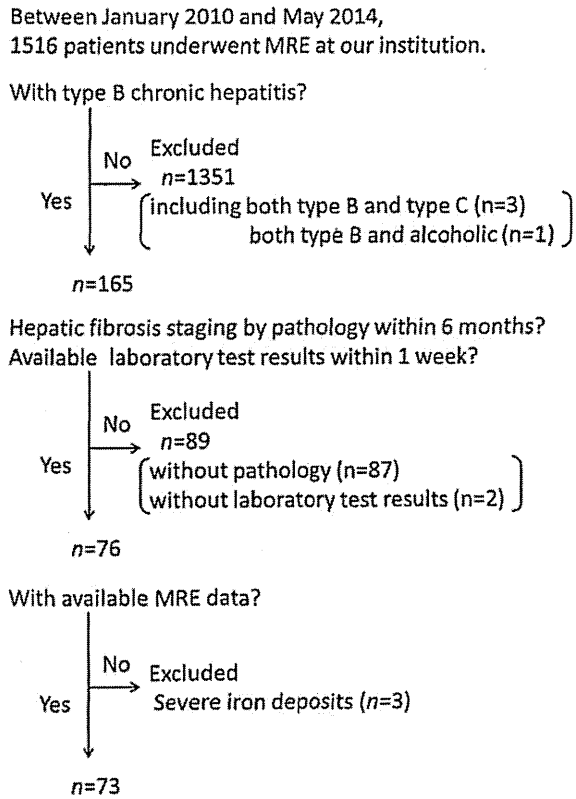

Fig. 1. Inclusion criteria applied prior to study participant enrollment.

Table 1. Sequence parameters of MRE

Parameter	1.5T system	3T system
Sequence	Two-dimensional gradient-echo T_1-weighted imaging	Two-dimensional gradient-echo T_1-weighted imaging
Plane	Transverse	Transverse
Repetition time (ms)	100	50
Echo time (ms)	27	20
Matrix	256 × 64	256 × 80
Field of view (cm)	36 × 27	35 × 35
Section thickness/intersection gap (mm)	10/5	10/5
Number of signals acquired	1	1
Flip angle (°)	30	23
Acquisition time (s)	13	17
Frequency of driver (Hz)	60	60
Amplitude (%)	60	70
Axis of motion-sensitizing gradient pulse	z	z

MRE; magnetic resonance elastography

30 patients and resection in 43. One of 3 pathologists with 12 to 18 years of experience who was blinded to the MRE results reviewed all specimens by evaluating hematoxylin and eosin staining and Masson trichrome staining to determine the stage of fibrosis using the METAVIR scoring system. According to the scoring system, F0 indicated no fibrosis (n = 0); F1, portal fibrosis without septa (n = 13); F2, portal fibrosis with a few septa (n = 17); F3, numerous septa without cirrhosis (n = 16); and F4, cirrhosis (n = 27).

Serum fibrosis markers

The values for the serum fibrosis markers, AAR, APRI, FIB-4 index, and FibroQ, were calculated using the following formulas, where ULN denoted the upper limit of normal AST levels, PLT referred to the platelet count, and PT-INR signified the prothrombin time-international normalized ratio:

$$AAR = \frac{AST[U/L]}{ALT[U/L]};\ APRI = \frac{AST[U/L]/ULN}{PLT[10^9/L]} \times 100;$$

$$Fib-4\ index = \frac{age[years] \times AST[U/L]}{PLT[10^9/L] \times ALT^{1/2}[U/L]};$$

and

$$FibroQ = \frac{10 \times age[years] \times AST[U/L] \times PT-INR}{PLT[10^9/L] \times ALT[U/L]}.$$

Magnetic resonance elastography

MRE was performed using either a 1.5-tesla (T) MR system with a superconducting magnet (Signa Excite HD MR 1.5T, GE Medical Systems, Waukesha, WI, USA) with an 8-channel phased-array coil (n = 57) or a 3T MR system (Discovery 750; GE Medical Systems) with a 32-channel phased-array coil (n = 16). Patients were placed in the supine position, and a cylindrical passive driver was attached to the right chest wall using a rubber belt. A pneumatic vibration was delivered through a plastic cylinder to the driver via a vibrator placed outside the imaging room. The driver then transferred the vibration to the liver via the chest wall.[26] The scanning position began above the gallbladder and progressed to below the subphrenic region of the liver. Patients were instructed to hold their breath after expiration to maintain a consistent position during image acquisition at each phase offset.[14]

Table 1 summarizes the MR sequence parameters. The MR scanners automatically generated liver stiffness maps by processing the acquired propagating shear wave images according to a 2-dimensional (2D) inversion algorithm,[27] and shear stiffness of the tissue was translated to a pixel value (kPa).[28]

On the basis of the stiffness maps, 2 radiologists (S.I., H.M.), each of them had 9 years experiences in abdominal radiology, who were blinded to the histopathological data placed a region of interest (ROI) in the right lobe of the liver of each patient. The latest versions of MRE systems automatically provide confidence maps that indicate areas that are inadequate for measurement as areas of cross-hatching on stiffness maps. However, we stuck with placing ROIs only with wave images and stiffness map for consistent measurement without using confidence maps. We placed ROIs of at least 1.5

cm^2 to exclude blood vessels seen on a magnitude image of MRE and the edge of the liver and to include a parallel wave form without interference on the phase images (Fig. 3).

Statistical analysis

We calculated the mean and standard deviation of the serum fibrosis markers and of the liver stiffness values measured by Observers 1 and 2 for each stage of hepatic fibrosis. Spearman's rank correlation was used to determine significant correlation of the variables with the stage of hepatic fibrosis. The correlation was deemed strong if the absolute value of the coefficient ($|\rho|$) exceeded 0.7, moderate if the value was greater than 0.4 and less than or equal to 0.7, minimal if the value was greater than 0.2 and less than or equal to 0.4, and not meaningful if the value was 0.2 or less. The discriminative capacities of the serum fibrosis markers and the MRE images were assessed using receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (Az value) and the optimal cutoff value were calculated to differentiate ≥ F2 from ≤ F1, ≥ F3 from ≤ F2, and F4 from ≤ F3. We used the jack knife method to compare the Az values of serum fibrosis markers and MRE measurements determined by each observer to discriminate the stage of fibrosis.[29] We also used intraclass correlation coefficients (ICC) to assess interobserver agreement. Agreement was considered excellent with an ICC value (r) above 0.8, good with a value above 0.6 and less than or equal to 0.8, moderate with a value above 0.4 and less than or equal to 0.6, fair with a value above 0.2 and less than or equal to 0.4, and poor with a value of 0.2 or less.

We analyzed all statistics using JMP software (Ver. 10; SAS Institute, Cary, NC, USA) and employed 2 one-sided t-tests that assumed 0.1 kPa as a clinically acceptable difference between the observers to determine statistical equivalence between the results of the 2 observers. P values < 0.05 were considered statistically significant.

Results

Relationships between stage of fibrosis, liver stiffness, and serum fibrosis markers

Table 2 summarizes serum fibrosis marker and liver stiffness data. Mean liver stiffness values determined by MRE increased with the stage of fibrosis (Fig. 2a, b), and interobserver correlations were strong (Observer 1, $\rho = 0.9029$, $P < 0.0001$; Observer 2, $\rho = 0.8855$, $P < 0.0001$).

There was a moderate positive correlation between APRI and stage of fibrosis ($\rho = 0.4051$, $P = 0.0004$) but only minimal correlation between FibroQ and fibrosis stage ($\rho = 0.2195$, $P = 0.0620$) (Fig. 2c, f). No significant correlations were observed between Fib-4 index and stage of fibrosis ($\rho = 0.1831$, $P = 0.1211$; Fig. 2d) and AAR and stage of fibrosis ($\rho = -0.0087$, $P = 0.9420$; Fig. 2e). Figure 3 details the clinical cases.

Diagnostic values of serum fibrosis markers and MRE

The discrimination ability of MRE and serum fibrosis markers are shown in Table 3 (Observer 1) and Table 4 (Observer 2). According to ROC analysis, the MRE Az values determined by Observers 1 and 2 for the diagnosis of each stage of fibrosis were significantly higher than the fibrosis marker values. The cutoff values for Observer 1

Table 2. Comparison between liver stiffness and serum fibrosis markers for each fibrosis stage

	F1	F2	F3	F4	ρ	P value
liver stiffness (kPa) (observer 1)	2.50 ± 0.36	2.99 ± 0.44	3.82 ± 0.51	5.35 ± 0.98	0.9029	<0.0001*
liver stiffness (kPa) (observer 2)	2.58 ± 0.31	3.04 ± 0.44	3.83 ± 0.59	5.32 ± 1.03	0.8855	<0.0001*
APRI	0.57 ± 0.25	0.65 ± 0.36	0.77 ± 0.47	1.11 ± 0.63	0.4051	0.0004*
Fib-4 index	1.49 ± 1.11	0.97 ± 0.41	1.30 ± 0.98	1.54 ± 0.92	0.1831	0.1211
AAR	1.34 ± 0.54	1.10 ± 0.34	1.17 ± 0.38	1.21 ± 0.42	−0.0087	0.9420
FibroQ	8.30 ± 6.74	5.25 ± 2.60	7.77 ± 5.81	8.71 ± 5.05	0.2195	0.0620

Statistical analysis was performed using the Spearman's correlation analysis. Data are presented as mean ± standard deviation

ρ means Speaman's correlation coefficient

APRI, aspartate aminotransferase (AST)-to-platelet ratio index; AAR, AST/alanine aminotransferase (ALT) ratio; FibroQ, fibrosis quotient.

* Liver stiffness and APRI increased as the liver fibrosis stage progressed ($p < 0.05$).

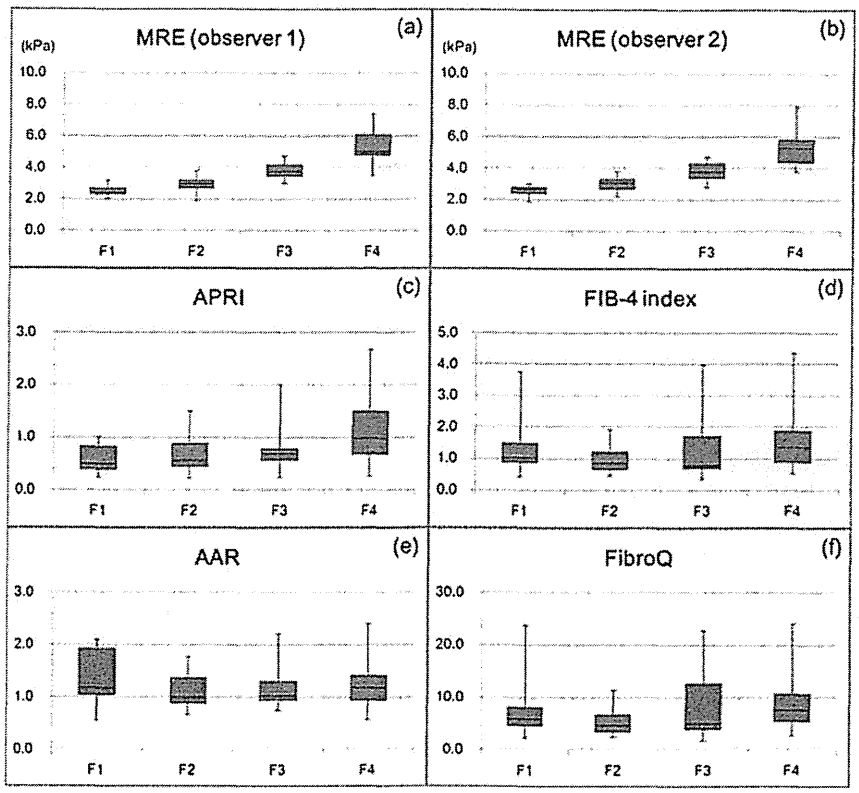

Fig. 2. Box-plot of stiffness values measured by magnetic resonance elastography (MRE) and correlation of serum fibrosis markers with stage of fibrosis. Box-plot of MRE stiffness values for (a) Observer 1 and (b) Observer 2. The mean stiffness values of the liver increased as the stage of fibrosis progressed, and the correlation was strong (Observer 1, $\rho = 0.9029$, $P < 0.0001$; Observer 2, $\rho = 0.8855$, $P < 0.0001$). (c) A moderately positive correlation was detected between the aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and fibrosis stage ($\rho = 0.4051$, $P = 0.0004$); (d) fibrosis 4 (Fib-4) index; (e) and AST-to-alanine aminotransferase (ALT) ratio (AAR). (f) A minimal correlation was detected between the fibrosis quotient (FibroQ) and stage of fibrosis ($\rho = 0.2195$, $P = 0.0620$). No significant correlations were observed between the Fib-4 index and stage of fibrosis ($\rho = 0.1831$, $P = 0.1211$) and AAR and stage of fibrosis ($\rho = -0.0087$, $P = 0.9420$).

were ≥ F2, 3.0 kPa; ≥ F3, 3.4 kPa; and F4, 4.5 kPa. Those for Observer 2 were ≥ F2, 3.1 kPa; ≥ F3, 3.4 kPa; and F4, 4.0 kPa.

Interobserver agreement of MRE

The interobserver ICC was excellent for Observers 1 and 2 (0.971; 95% CI, 0.955 to 0.982). Figure 4 shows scatter plots generated to visualize correlations and Bland-Altman plots created to visualize the dispersion of liver stiffness measurements of the 2 observers. The average (95% CI) difference in liver stiffness between the observers was 0.0178 (−0.0568 to 0.0924). Liver stiffness measured by both observers was statistically equivalent within ± 0.1 kPa, which suggested that the mean difference in measurements by the 2 observers was less than 0.1 kPa ($P = 0.0157$).

Discussion

Our results revealed the superior discriminative ability of MRE to serum fibrosis markers for determining the stage of hepatic fibrosis in patients with CHB, indicated high interobserver agreement for MRE-based measurements of liver stiffness measurements.

The results of the current study were in accord with findings of previous reports that showed the superiority of MRE with regard to discriminative ability for staging liver fibrosis compared to serum fibrosis markers. It has been reported that assessments of serum fibrosis markers are simple and rel-

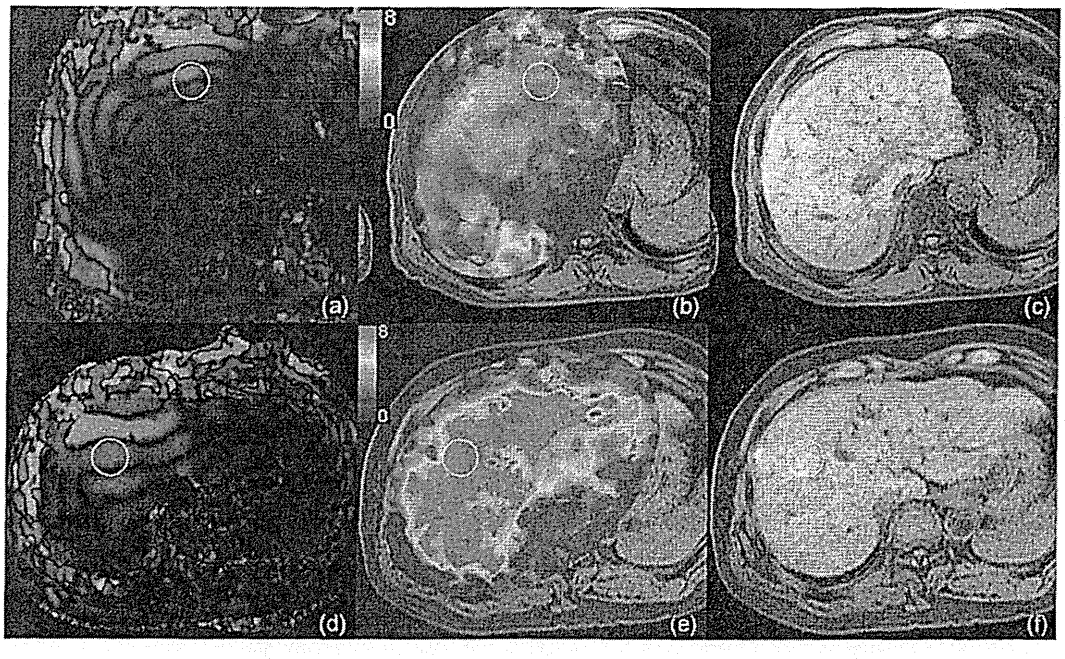

Fig. 3. Magnetic resonance elastography (MRE) images of 2 patients, (**a-c**) a 62-year-old man with mild fibrosis (F1) and (**d-f**) a 58-year-old man with cirrhosis (F4). (**a** & **d**) Phase images; (**b** & **e**) portions of the elastogram that correspond with the liver superimposed on conventional MR images; (**c** & **f**) magnitude images. A region of interest (ROI) was placed in the right lobe of the liver (circle) based on the criteria that the ROI was at least 1.5 cm^2, excluded blood vessels seen on the magnitude image of MRE, excluded the edge of the liver, and included a parallel wave form without interference on the phase images. The mean liver stiffness values increased with the progression of the stage of fibrosis.

Table 3. Comparison between MRE measured by observer 1 and serum fibrosis markers

Variable	MRE (observer 1)	APRI	Fib-4 index	AAR	FibroQ
F1 vs F2–4					
Az value (95%CI)	0.945 (0.862–0.979)	0.668 (0.505–0.799)	0.523 (0.345–0.695)	0.583 (0.383–0.760)	0.496 (0.318–0.676)
P value (vs MRE)	—	<0.0001	<0.0001	<0.0001	<0.0001
F1–2 vs F3–4					
Az value (95%CI)	0.974 (0.928–0.991)	0.697 (0.562–0.991)	0.595 (0.459–0.719)	0.491 (0.355–0.629)	0.632 (0.494–0.751)
P value (vs MRE)	—	<0.0001	<0.0001	<0.0001	<0.0001
F1–3 vs F4					
Az value (95%CI)	0.978 (0.927–0.994)	0.742 (0.602–0.845)	0.647 (0.511–0.764)	0.519 (0.383–0.653)	0.649 (0.512–0.765)
P value (vs MRE)	—	0.0003	<0.0001	<0.0001	<0.0001

PPV, positive predictive value; NPV, negative predictive value.
APRI, aspartate aminotransferase (AST)-to-platelet ratio index; AAR, AST/alanine aminotransferase (ALT) ratio; FibroQ, fibrosis quotient.
Az values are shown with 95% confidence interval.
Az values of MRE and serum fibrosis markers for discriminating the fibrosis stages were compared using jackknife method.

Table 4. Comparison between MRE measured by observer 2 and serum fibrosis markers

Variable	MRE (observer 2)	APRI	Fib-4 index	AAR	FibroQ
F1 vs F2–4					
Az value (95%CI)	0.936 (0.858–0.973)	0.668 (0.505–0.799)	0.523 (0.345–0.695)	0.583 (0.383–0.760)	0.496 (0.318–0.676)
P value (vs MRE)	—	0.0002	<0.0001	0.0004	<0.0001
F1–2 vs F3–4					
Az value (95%CI)	0.967 (0.913–0.988)	0.697 (0.562–0.991)	0.595 (0.459–0.719)	0.491 (0.355–0.629)	0.632 (0.494–0.751)
P value (vs MRE)	—	<0.0001	<0.0001	<0.0001	<0.0001
F1–3 vs F4					
Az value (95%CI)	0.967 (0.914–0.987)	0.742 (0.602–0.845)	0.647 (0.511–0.764)	0.519 (0.383–0.653)	0.649 (0.512–0.765)
P value (vs MRE)	—	0.0004	<0.0001	<0.0001	<0.0001

PPV, positive predictive value; NPV, negative predictive value.
APRI, aspartate aminotransferase (AST)-to-platelet ratio index; AAR, AST/alanine aminotransferase (ALT) ratio; FibroQ, fibrosis quotient.
Az values are shown with 95% confidence interval.
Az values of MRE and serum fibrosis markers for discriminating the fibrosis stages were compared using jackknife method.

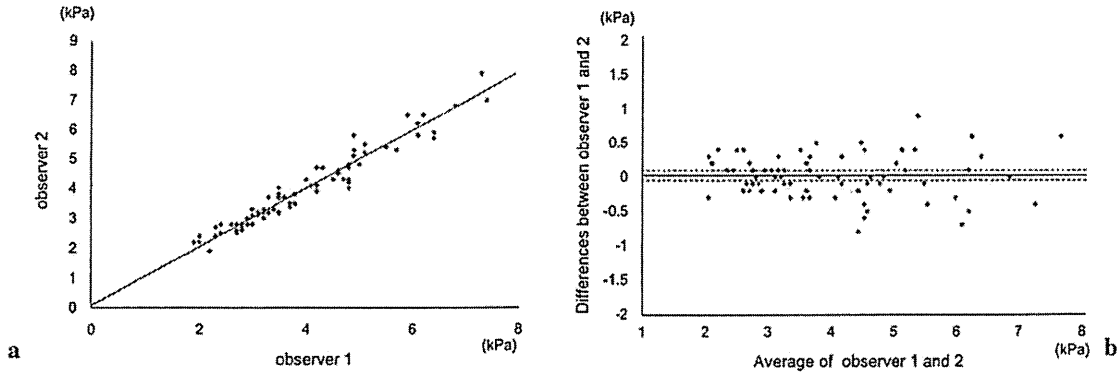

Fig. 4. Scatter plots and Bland-Altman plots. (**a**) Linear regression of the results from the 2 observers. The intraclass correlation coefficient was 0.971 (95% confidence interval [CI], 0.955 to 0.982). (**b**) Bland-Altman plots show the distribution of the difference in 2 measurements by different observers. The central line reflects the mean difference, and the top and bottom broken lines correspond with the 95% limits of the mean difference. The mean difference between the 2 observers was statistically equivalent within ± 0.1 kPa ($P = 0.0157$).

atively reliable methods for estimating stage of fibrosis.[30] Conversely, serum markers are associated with limited discriminative ability for staging liver fibrosis. Further, their validity decreases when patients have no underlying liver disease or when serum AST levels are normal.[31] Previous systemic reviews of the performance of serum fibrosis markers revealed that the median Az values for discriminating stages of liver fibrosis ranged from 0.73 to 0.88 for ≥ F2 and from 0.73 to 0.94 for discriminating F4.[32–34] However, in the current and previous reports, the capacity to discriminate stages of liver fibrosis was consistently higher for MRE than fibrosis markers.[13,17,35,36]

Our cut-off values in subjects were in accord with those reported by Venkatesh and associates[17] but lower than the values reported by Shi's group,[18] even though both studies involved CHB patients. Hepatitis activity may be a confounder of liver stiffness measurement during liver fibrosis staging using MRE.[37] However, the higher stiffness values observed by Shin and colleagues than ours even

among patients with mild hepatitis suggest that the discrepancy cannot be explained by inflammation alone. We might have to consider other confounding factors, including differences in MR unit/coil or parameters. We observed mean liver stiffness values that were relatively lower (by a margin of 0.2 to 0.8 kPa) than those of other studies conducted in patients with CHC,[13] and the current mean values were also lower for each stage of fibrosis than those in prior studies involving multiple etiologies.[38,39] Besides the technical aspects of MRE, the differences might be related to multiple factors, including pattern of pathological fibrosis (micronodular versus macronodular cirrhosis), variation in pathological assessment, and difference in the patient population.[40,41]

Consistency in measurement is critically important for quantitative assessments including MRE.[10,12,42] Hines's group revealed only a minor effect of interobserver variability on overall variability of measurements using a linear mixed effect model in which the component sources of variability included day-to-day physiological changes in the subject and examinations were replicated on the same subject on the same day.[11] In addition, Shin's group recently reported a very low interobserver difference in stiffness measurements (~0.005 kPa) in healthy subjects.[43] Although we observed statistically equivalent liver stiffness measurements by the 2 observers (within a difference of 0.1 kPa), the mean of the difference (0.0178 kPa) was relatively higher than values reported by Shin. Our lower interobserver agreement might be attributable to variations in measurements resulting from the heterogeneous fibrosis patterns detected in the liver. However, the difference we observed in interobserver agreement might be acceptable because the value was smaller than the difference between the results of short term (a week, ~0.05 kPa) or mid-term (a half year, ~0.05 kPa) repetitions of MRE in healthy subjects.[43]

In addition to MRE, several other MR imaging methods have been proposed for staging hepatic fibrosis, including diffusion-weighted imaging, intravoxel incoherent motion, and an uptake index in gadoxetic acid-enhanced hepatocyte-phase imaging.[44–47] The alternative methods employ such parameters as molecular diffusivity, tissue microperfusion, or hepatocyte function to assess hepatic fibrosis. Although results using these methods correlate well with the stage of fibrosis, comparative studies have suggested the inferior diagnostic capabilities of these methods to the use of serum markers or MRE.[35,46,48,49] Ultrasound-based elastography, another method used to measure liver stiffness, includes transient elastography (FibroScan®, Echosens™, Paris, France),[50] real-time strain elastography (RTE),[51] acoustic radiation force impulse (ARFI),[52] and real-time share wave elastography (SWE).[53] In previous studies, ultrasound-based elastography performed well in predicting hepatic fibrosis.[54–66] However, only a limited number of clinical studies have compared the discriminative abilities of MRE and ultrasound-based elastography for staging hepatic fibrosis.[58–60,66] Two of those revealed the superior ability of MRE to Fibroscan® for distinguishing stages of hepatic fibrosis,[58,60] and the others revealed the similar diagnostic performance of MRE, Fibroscan®, and SWE for staging hepatic fibrosis.[59,66] Consequently, it might be concluded that the discriminative ability of MRE for staging hepatic fibrosis is equivalent or superior to that of ultrasound-based elastography. However, no clinical guideline is available for these new techniques for noninvasive assessment of liver fibrosis. Further, a prospective validation study that combines these methods would offer comfortable and low risk management of liver disease.[67,68]

The current study had some limitations. First, we included no F0 case because of the minimal clinical requirement for performing a biopsy to evaluate fibrosis during early stages of liver disease. Second, we did not analyze necroinflammation (A grade in the METAVIR scoring system); some studies have shown that the grade of hepatitis activity independently affected MRE measurements of liver stiffness. Further, we did not subdivide cases by grade because our patient population was moderate in size. Third, only one histopathological assessment was used to diagnose the stage of fibrosis following either liver biopsy or resection. In addition, subjects underwent scanning on 2 different MR scanners, though the difference in main magnetic field strength or differences in coil channels should not theoretically affect the MRE stiffness measurement.[69] Neither should MR parameter settings, including repetition time (TR) and echo time (TE), affect the measurement results. However, a recent study suggested that slightly different stiffness values may be obtained using different parameter settings.[70] Therefore, it would be necessary to show the reproducibility of the MRE results using various field strengths and scanners from different manufacturers to validate the accuracy and reproducibility of MRE.

Conclusion

In conclusion, MRE proved to be a reliable tech-

nique for discriminating the stage of hepatic fibrosis in patients with CHB.

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急性胆管炎の重症度判定：Endotoxin Activity Assay

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索引用語：急性胆管炎，エンドトキシン血症，Endotoxin Activity Assay，DIC，血液培養

1 急性胆管炎とエンドトキシン血症

Levinら[1]が急性胆管炎症例の血中からエンドトキシンを初めて証明して以来，エンドトキシンが胆管炎を重篤化する直接の因子として注目され今日まで至っている．胆管炎におけるエンドトキシン血症の発生機序は胆管内圧上昇によるcholangio-venous reflux[2]と胆管炎による肝膿瘍からの直接的感染と考えられている[3]．

急性胆管炎の死亡率は1980年以前では50％[4,5]とされていたが，2000年以降では2.7～10％[6,7]と報告されている．また急性胆管炎の原因は，かつては総胆管結石症の頻度が最も高かったが，近年は悪性疾患の占める割合が増えている．膵・胆道悪性疾患患者は化学療法中の胆管炎や胆管ステント閉塞による胆管炎，胆管造影後の胆管炎，術後胆管炎などの医療関連胆管炎をしばしば発症するため，耐性菌が増えていることも治療において重要な点である．

Tokyo Guidelines 2013（TG13）[8]における急性胆管炎の重症度は軽症，中等症，重症と分類されている．軽症は基本的には保存的治療が可能，中等症は臓器障害に陥っていないが早期に胆道ドレナージが必要，重症は臓器障害をきたしているためIntensive careのもとに緊急胆道ドレナージが必要であるとされている．胆道ドレナージの方法は外科的，経皮経肝，内視鏡ドレナージがあり，最も低侵襲な内視鏡ドレナージが第一選択とされている．近年では内視鏡手技の向上により胆道再建術後にバルーン小腸内視鏡的ドレナージ，経乳頭的ドレナージが困難な症例には超音波内視鏡ガイド下経胃または経十二指腸胆管ドレナージが行われてきており，より低侵襲な治療が可能となってきている．

急性胆管炎の治療成績はDICおよび臓器不全に左右されるといわれており[3]，DICを合併する原因にはエンドトキシン血症が深く関係している．すなわちエンドトキシンにより活性化された単球がTNF-αなどの炎症性

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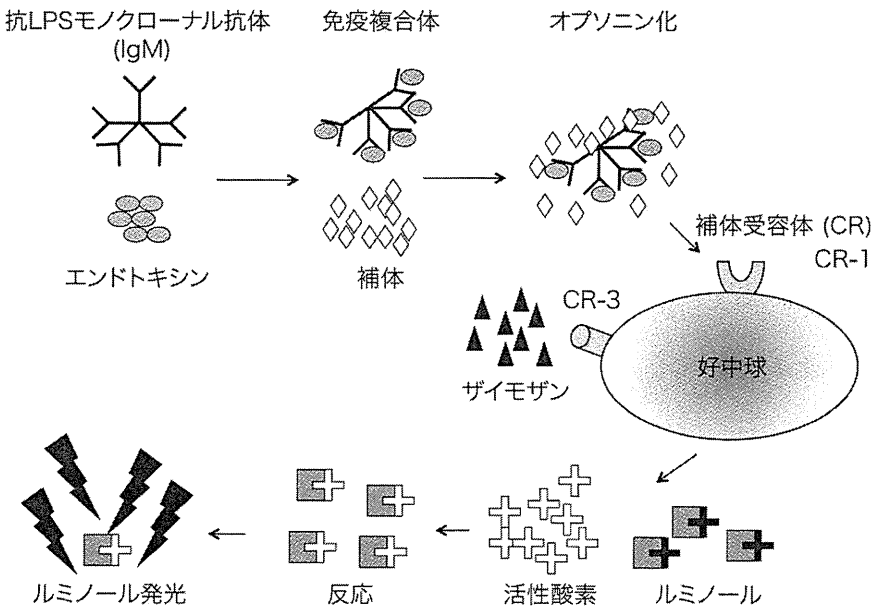

図1　Endotoxin Activity Assay（EAA）法の原理

特異的なモノクローナル抗体とエンドトキシンとの免疫複合体に補体が結合することでオプソニン化が起こる．オプソニン化により貪食されやすくなった免疫複合体を好中球が取り込むことで活性酸素を産生する．またザイモザンも好中球に取り込まれ活性酸素産生を増強する．この活性酸素と試薬中のルミノールを結合させルミノメーターで測定する方法である．

サイトカインを放出し，それが血管内皮細胞や好中球に作用した結果，Tissue Factor（TF）の発現増加を導くとともにThrombomodulin（TM），Tissue Plasminogen Activator（tPA）の産生低下が惹起される．その結果，血管内皮細胞障害による抗血栓作用が抑制されるため血管内凝固が発生し微小循環障害を認める結果DICに陥ると考えられている[9]．

よって急性胆管炎においてエンドトキシン血症を正確に評価することが，重症度評価や予後予測に有用な可能性が考えられている[10]．

2　エンドトキシン測定

エンドトキシンの測定法はリムルス法（以下LAL法）が一般的に行われてきた．1956年にBangら[11]によりカブトガニの血液がvibrio菌の感染でゲル状に固まることが発見され，以来この反応を利用した測定法の検討が進み，1980年代にはカブトガニ血球抽出物から調製された高感度のエンドトキシン測定試薬（LAL試薬）が普及した．急性胆管炎における血中エンドトキシンの測定では，LAL法で測定したエンドトキシン値が上昇する[12]と報告しているものもあれば上昇しないという報告[13,14]もあり一定の見解はない．また急性胆管炎の予後と血中エンドトキシン値との関係に相関はみられず，エンドトキシン値の低下が予後改善にはつながらない[15]との報告がある．その一方で同じエンドトキシン血症を伴った髄膜炎においては血中エンドトキシン値が予後に関係すると報告されており[16]，従来のLAL法によるエンドトキシン値が真にエンドトキシン血症の病態を反映しているかは議論の多い点である[17]．

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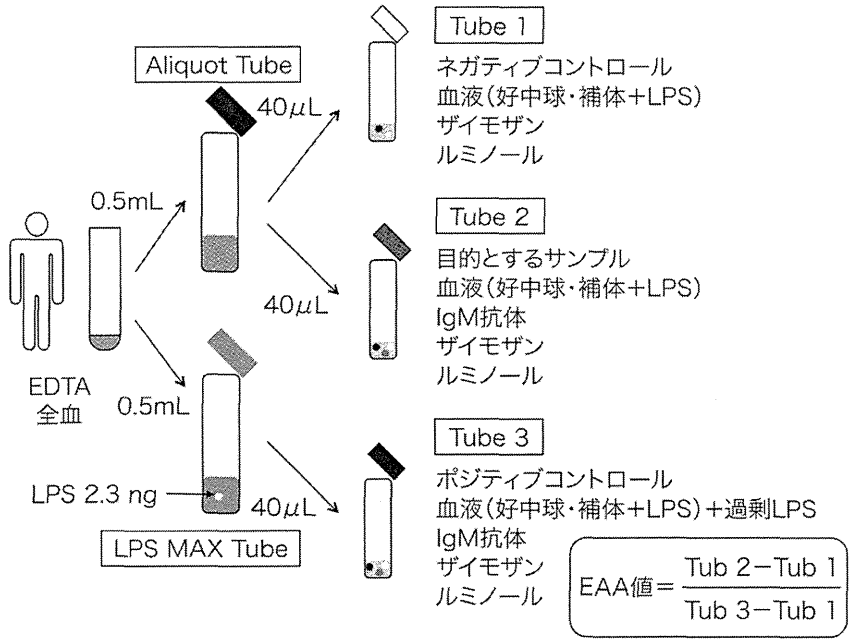

図2　EAAの測定方法

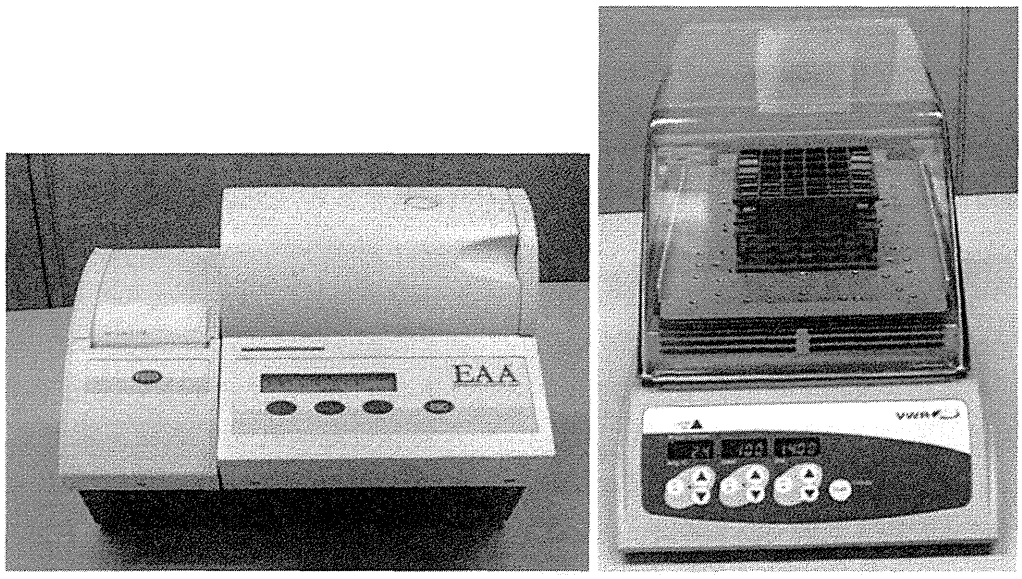

図3　左：ルミノメーター（Berthold社製 Smartline Line TL），右：加温振盪機（インキュベーター）（VWR社製 Incubating Mini Shaker）

3　Endotoxin Activity Assay法

1998年にRomaschinらが報告したEndotoxin Activity Assay（以下EAA）法（図1）[18]は，リムルス反応を利用しない測定法で，血中のエンドトキシン活性を好中球の反応を介して間接的に測定する方法である（図2）．

北米および欧州の10施設で行われたMEDIC StudyではEAAがグラム陰性菌感染の有無やAPACH Ⅱスコアおよび重症化のリスクに相関したと報告されている[19]．ICU入院患者においては入院時のEAA値がAPACH Ⅱスコアや28日死亡率と相関するという報告[20]や，術後のEAA高値患者はICU滞在日数が

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表1　患者背景

患者背景 (n = 235)			人数(%)
年齢 (歳)*			70.0±10.7
性別，男性			167 (71.1)
肝膿瘍合併			27 (11.5)
急性期DICスコア*			2.0±1.94
SOFAスコア*			2.0±2.02
敗血症重症度 (SSCG)			
	non-SIRS		77 (32.8)
	Sepsis		45 (19.1)
	Severe sepsis		103 (43.8)
	Septic shock		10 (4.3)
急性胆管炎重症度(TG13)			
	軽症		75 (31.9)
	中等症		113 (48.1)
	重症		47 (20.0)
在院日数*		中央値±標準偏差	10.0±16.5
28日死亡			10 (4.2)

*中央値±標準偏差
SOFA：Sequential organ failure assessment，SSCG：Surviving Sepsis campaign Gideline，TG13：Tokyo Guidelines 2013

長いこと[21]，胆道感染症でEAA高値群は血液培養検査の陽性率が高く，在院日数が長いこと[13]が報告されている

EAA (Spectral Diagnostics，Toronto，Canada) の測定は，EAA試薬(Spectral Diagnostics社)，ルミノメーター (Berthold Detection System，Pforzheim，Germany)，加温振盪機(VWR社製 Incubating Mini Shaker) (図3) を用いる．患者から2 mLの全血をEDTA入り滅菌採血管に採血し3時間以内に測定を行う．エンドトキシンフリー試験管 (Aliquot tubes) と極量に相当するEscherichia coli 2.3 ng相当のLipopolysaccharide (LPS)添加試験管 (LPS max tubes)にそれぞれ採取した全血0.5 mLずつを添加し，37度で10分間インキュベートする．Aliquot tubesから40 μLずつTube 1とTube 2に，LPS max tubesから40 μLをTube 3に入れる．Tube 2とTube 3には2.6 μg/mLの抗エンドトキシン抗体が添加されている．またTube1, Tube 2, Tube 3にはルミノールおよびザイモザンが添加されている．Tube 1，Tube 2，Tube 3を37度で14分間振盪しながらインキュベートしルミノメーターでTube1，Tube 2，Tube 3を測定する．Tube 1は血液中の好中球自体の非特異的反応を反映したnegative control，Tube 3は最大量のLPSで刺激された好中球反応を反映したpositive controlとし，Tube 2は患者血液中のエンドトキシンによって刺激された好中球の反応を反映している．EAA値＝(Tube 2–Tube 1) /

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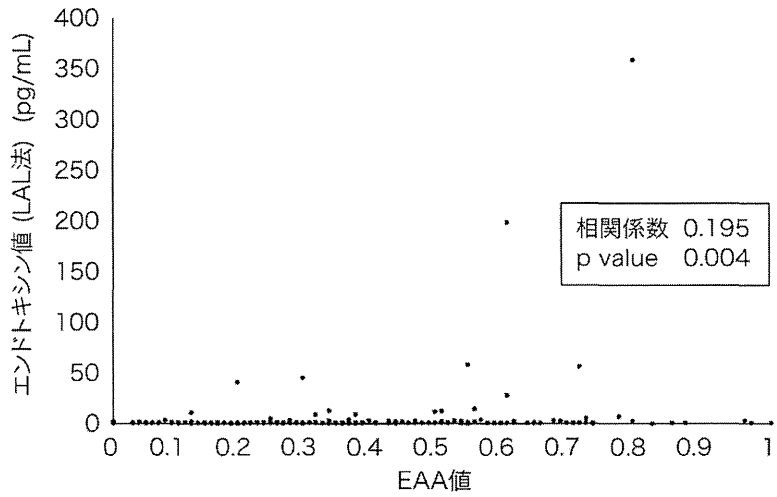

図4　リムルス法（LAL法）エンドトキシン値とEAA値の関係
LAL法によるエンドトキシン値とEAA値は相関係数0.195と相関関係は認めなかった.

（Tube 3–Tube 1）としEAA値は0～1の相対値となる.

手技に熟練すれば1時間以内で測定でき手技も簡便であるため迅速に結果を得ることができ速やかに治療に活用することができるという利点がある.

4 教室における急性胆管炎の検討

当科では急性胆管炎患者のEAAを測定しほかの炎症性マーカーや敗血症および胆管炎重症度との相関，予後予測因子としての有用性について検討を行っている.

2011年6月～2014年12月までに急性胆管炎の診断で当科に入院し治療を行った235例を対象とし，入院時，入院後1日目，5日目，10日目にEAAおよび白血球数，血小板数，凝固因子，C-reactive protein（CRP），プロカルシトニン測定を行った．また全例入院時に血液培養検査を2セット採取し，胆管炎重症度[8]，日本救急医学会の急性期DICスコア[22]，the Sequential Organ Failure Assessment Score（SOFAスコア）[23]を評価した.

患者の内訳（表1）は軽症胆管炎31.9％（75/235例），中等症胆管炎48.1％（113例），重症胆管炎20.0％（47例）であった．肝膿瘍合併胆管炎は11.5％（27例）に認めた．LAL法で測定したエンドトキシン値が1.0 pg/mL以上の症例は24.3％（54/222例）であったがEAA値との相関は認めなかった（図4）.

EAA値を低値群（EAA値＜0.4）162例，高値群（EAA値≧0.4）73例に分けて比較すると白血球数やPT-INRでは両群に差は認めないものの高値群の方がCRP（p＝0.004），プロカルシトニン値（p＜0.001）が有意に高く，血小板数は有意に低値（p＝0.002）であった．血液培養陽性率は低値群が29.6％（48例）に対し，高値群は47.9％（35例）と有意に高率（p＝0.005）であった．その中でグラム陰性桿菌が占める割合は低値群では83.3％（40/48例），高値群では74.3％（26/35例）で有意な差は認めなかった（p＝0.41）.

重症度スコアや予後経過についてEAA値の低値群，高値群の両群を比較検討すると

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表2　EAA値低値群(EAA値＜0.4)および高値群(EAA値≧0.4)の比較

低値群と比較し高値群は急性期DICスコア，SOFAスコアが高値であり，重症胆管炎を有意に多く認めた．またCRP，プロカルシトニン値は高く血小板数は減少し，血液培養陽性率が有意に高かった．

	EAA値		p値
	EAA＜0.4 n＝162	EAA≧0.4 n＝73	
年齢*	60.5±10.5	69.0±11.1	0.41
性別，男性	115 (71.0)	52 (71.2)	0.55
肝膿瘍合併	15 (9.3)	12 (16.4)	0.087
急性期DICスコア*	1.0±1.75	2.0±2.23	0.02
急性期DICスコア≧4	29 (17.9)	25 (34.2)	0.006
DIC持続日数*	3.0±7.37	7.0±6.35	0.17
SOFAスコア*	2.0±1.66	3.0±2.53	0.001
SOFAスコア≧5	10 (6.2)	15 (20.5)	0.001
敗血症重症度 (SSGA)			0.69
non-SIRS	53 (32.7)	24 (32.9)	
Sepsis	34 (21.0)	11 (15.1)	
Severe sepsis	69 (42.6)	34 (46.6)	
Septic shock	6 (3.7)	4 (5.5)	
急性胆管炎重症度　(TG13)			0.009
軽症＋中等症	137 (84.6)	51 (69.9)	
重症	25 (15.4)	22 (30.1)	
白血球数 (/μL)*	9,100±4,433.3	7,700±7,889.9	0.3
CRP (mg/dL)*	4.40±5.35	6.77±6.75	0.004
プロカルシトニン値 (ng/mL)*	0.62±12.03	1.73±23.64	<0.001
血小板数 (×10,000/mL)*	17.6±8.07	13.2±8.74	0.002
PT-INR*	1.18±0.30	1.23±0.40	0.068
血液培養陽性症例数	48 (29.6)	35 (47.9)	0.005
在院日数*	10.0±14.94	12.0±19.42	0.077
28日死亡	5 (3.1)	5 (6.8)	0.16

*中央値±標準偏差

(表2)入院時の急性期DICスコア，SOFAスコア，胆管炎重症度は低値群より高値群の方が有意に重症度が高いという結果を認め，EAA値は急性胆管炎の重症度を反映している結果となった．またDIC持続期間，在院日数についても統計学的有意差はないが高値群で長い傾向がみられることからEAA値は予後予想にも有用かもしれない．

5　おわりに

EAA高値群の方が低値群と比較して，CRPやプロカルシトニンといった炎症性マーカーが高値であった．また血液培養陽性率も有意に高かった．問題点は血液培養検査でグラム陽性菌陽性例でもEAA値が高値である症例が認められたことである．EAA値はエンド

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トキシンを直接的に測定しているのではなく，好中球の反応を介して測定しているため，グラム陽性球菌による敗血症で産生されたサイトカインやケモカインがEAA値に影響を与えている可能性も考えられ，その評価は慎重に行う必要がある．

今回の検討ではEAA値はDIC持続期間や在院日数，死亡率といった予後に関して統計学的に有意な結果を得ることができなかったものの，高値群の方が長期間となる傾向を認めたことから，今後症例を重ねることで急性胆管炎の予後予測因子となる可能性は十分にあると考えている．

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■ 症例報告

腹部造影超音波検査が有用であった 生体肝移植後門脈体循環の盗血の1例

安井稔博，宇賀菜緒子，直江篤樹，渡邉俊介，原普二夫，鈴木達也

Usefulness of abdominal contrast enhanced ultrasonography for diagnosis of the portosystemic shunt after a living donor liver transplantation

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【Summary】

A portosystemic shunt remaining after a living-donor liver transplantation sometimes causes a postoperative portal venous flow drop. It is diagnosed with Doppler ultrasound, angiography, contrast-enhanced computed tomography or magnetic resonance angiography. We report a case in which a contrast-enhanced ultrasound was useful to find out a portosystemic shunt. The patient is an 8-year-old girl who had undergone a portoenterostomy for biliary atresia and a living-donor liver transplantation for a hepatopulmonary syndrome at that age of 8 years. Because of an ABO incompatible transplant, a catheter was inserted into the portal vein for local infusion therapy. At first, a Doppler ultrasound showed a normal portal venous flow. On the next day of removal of the portal venous catheter, however, her portal venous flow was not able to be confirmed. We supposed a portal thrombosis, but we were unable to confirm it by the contrast-enhanced CT scan. After a contrast-enhanced ultrasound was performed, we could confirm the portal venous flow and the steal of the portal blood through the remaining portosystemic shunt. In conclusion, a contrast-enhanced ultrasound is useful for the blood flow evaluation after a living-donor liver transplantation.

Keywords: living-donor liver transplantation, portosystemic shunt, contrast-enhanced ultrasound

Ⅰ．はじめに

小児生体肝移植術後の門脈合併症は約10%と報告されている[1,2]。術後血管合併症の早期発見のためのドップラー超音波検査は確立された手法であるが，血管の描出や正確な診断としては不十分な場合もある。近年，造影超音波が普及し始め，肝移植術後の早期血管合併症の評価においても造影超音波検査の有用性を示した報告も見られるようになってきた[3-7]。今回，術後門脈体循環シャントのため，ドップラー超音波で血流を認めなくなった症例において，造影超音波により正確な血流評価をしえた症例を経験したため報告する。

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(2014・10・6受領；2014・12・29受理)

Ⅱ．症　例

症　例：8歳11カ月
主　訴：なし
既往歴：生後93日，胆道閉鎖症手術（葛西手術）
家族歴：なし
現病歴：生後93日に胆道閉鎖症に対して葛西手術を施行した。肝肺症候群が進行し肺内シャント率21%となったため，母をドナーとして肝左葉による生体部

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