Early detection of liver fibrosis with serum Mac-2 binding protein glycosylation-modified isomer (M2BPGi) during follow-up intestinal failure patients without intestinal failure-associated liver disease (IFALD)

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Abstract
Purpose Mac-2 binding protein glycosylation-modified isomer (M2BPGi) is a new marker for hepatic fibrosis progression. We examined the relationship between serum M2BPGi levels and liver histological findings in intestinal failure (IF) patients without IF-associated liver disease (IFALD).
Methods This study included IF patients without IFALD followed at our hospital. All patients underwent routine liver biopsies per protocol every 1–2 years. We examined M2BPGi levels and histological findings in relation to aspartate aminotransferase (AST) to platelet ratio index, fibrosis-4 index, and AST/ALT ratio. Liver fibrosis was evaluated based on the METAVIR score.
Results Total 18 liver biopsies out of eight patients were included. The median age was 11.5 years. Mean M2BPGi was 0.44 cutoff index (COI) in patients with F0 fibrosis, 0.78 COI in patients with F1 fibrosis and 1.63 COI in patients with F2 fibrosis. Mean M2BPGi was significantly higher in patients with F2 versus F1 or F0 fibrosis ($P < 0.016$ and $P < 0.028$, respectively). M2BPGi levels were more strongly correlated with fibrosis stage than with other conventional fibrosis markers.
Conclusion Serum M2BPGi is a novel marker of liver fibrosis in patients with IF. It is useful for follow-up prior to IFALD. Serum M2BPGi levels can support the interpretation of liver status.

Keywords Mac-2 binding protein glycosylation-modified isomer (M2BPGi) · Liver fibrosis · Intestinal failure-associated liver disease (IFALD) · Intestinal failure · Liver biopsy

Introduction
Intestinal failure (IF) is the inability of the gut to absorb nutrition, mostly due to short gut syndrome or motility disorder. Patients with IF are usually dependent on parenteral nutrition (PN). PN is a definitive therapy for these children. Home PN is the standard of care for children with IF [1]. The prognosis of persistent IF has improved due to the development of PN. However, prolonged PN causes numerous complications, including catheter-related sepsis and vital organ disorder.

Some patients might develop IF-associated liver disease (IFALD). IFALD is a potentially life-threatening complication [2]. IFALD progresses from mild periportal inflammation and cholestasis eventually to liver fibrosis and cirrhosis [3]. Especially in patients with severe liver fibrosis, it is difficult to treat with isolated intestinal transplantation alone; liver transplantation might also be needed. Therefore, evaluation of liver fibrosis during follow-up before the development of IFALD is critical. Liver biopsy (LBx) is the standard evaluation for liver fibrosis, but it is an invasive test that might cause serious complications [4]. Thus, noninvasive biomarkers have been explored.

Mac-2 binding protein glycosylation-modified isomer (M2BPGi) was recently established as a glycol biomarker
of liver fibrosis in patients with chronic hepatitis C [5]. M2BPGi has been shown to be a useful predictor in many chronic liver diseases. [6–9]. The usefulness of M2BPGi as a biomarker was demonstrated in pediatric biliary atresia [10]. However, there have been no available data regarding the relationship between serum M2BPGi levels and histological findings of liver fibrosis during regular follow-up of patients with IF prior to the development of IFALD.

Therefore, we focused on the serum liver fibrosis marker M2BPGi and compared it with the histopathological findings from percutaneous LBx. Thus, the aim of this study was to examine the relationship between serum M2BPGi levels and liver histological findings during regular follow-up of patients with IF before they develop IFALD.

**Methods**

**Patients**

Patients diagnosed with persistent IF but not IFALD who were followed at our hospital between May 2016 and February 2022 were included in this study. Patients who underwent LBx per protocol as part of the evaluation for intestinal transplantation were included. They underwent follow-up LBx every 1–2 years as candidates for isolated intestinal transplantation. We examined the relationship between M2BPGi levels and histological findings of liver fibrosis and compared them with other laboratory markers of liver fibrosis, including aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio, AST to platelet ratio index (APRI), and FIB-4 index. The APRI score was calculated using Wai’s formula: \[ \text{APRI} = \left( \frac{\text{AST}}{\text{upper limit of normal}} \right) / \text{platelet count (× 10⁹/L)} \times 100 \] [11]. The FIB-4 index was calculated using Sterling’s formula: \[ \text{FIB-4} = \frac{\text{age (years)} \times \text{AST (IU/L)}}{\text{platelet count (× 10⁹/L)} \times \sqrt{\text{ALT (IU/L)}}} \] [12].

Laboratory data were obtained within 3 months of LBx. Patients with C-reactive protein (CRP) over 1.00 mg/dL were excluded to avoid the effect of inflammation. Persistent IF was defined as IF patients required parental nutrition permanently. IFALD was defined as Total Bilirubin (TB) > 2.0 mg/dL. Patients with existing IFALD were excluded. This study examined whether liver fibrosis before reaching the IFALD stage could be detected.

**M2BPGi measurement**

Serum M2BPGi levels were measured using a two-site enzyme immunoassay. The assay reagent, which is commercially available in Japan, was purchased from Sysmex Corporation (Kobe, Japan). Quantification of M2BPGi was based on a lectin–antibody sandwich immunoassay using the fully automatic HISCL-800 immune analyzer (Sysmex Corporation). M2BPGi measurements were indexed with values obtained using the following equation: cutoff index (COI) = (M2BPGi) sample × (M2BPGi) NC [(M2BPGi) PC + (M2BPGi) NC], in which (M2BPGi) sample is the M2BPGi concentration in the serum sample, NC is the negative control, and PC is the positive control. The PC was supplied as a calibration solution preliminarily standardized to yield a COI value of 1.0 [5].

**Histological assessment**

LBx samples were assessed with hematoxylin–eosin and Masson’s trichrome stains. Percutaneous LBx was performed with a 16-gauge biopsy needle. All LBx were performed using an ultrasound-guided maneuver under either general anesthesia or intravenous sedation. The specimens were fixed in 4% phosphate-buffered formaldehyde and embedded in paraffin.

After hematoxylin–eosin and Masson’s trichrome staining, LBx specimens were examined microscopically. Experienced pathologists in our hospital evaluated the samples. Fibrosis was staged as F0–F4: F0, no fibrosis, F1 portal fibrosis without septa, F2 portal fibrosis with rare septa, F3 numerous septa without cirrhosis, and F4 liver cirrhosis [13].

No serious procedure-related complications were observed. In this study, progressive fibrosis was defined as ≥ F2. The presence of fibrosis was defined as ≥ F1.

**Statistical analysis**

Receiver operating characteristic (ROC) curve analysis was performed to calculate the area under the curve (AUC) for serum M2BPGi level and select the optimal cutoff value that maximized the sum of sensitivity and specificity for the presence of liver fibrosis (≥ F1) and progressive fibrosis (≥ F2) on histological examination. For continuous variables, comparisons among groups were performed using Student’s t test. Data are expressed as medians (range). \( P < 0.05 \) was considered statistically significant. Statistical analyses were performed with JMP 11 software (SAS Institute, Cary, NC, USA). This study was approved by our hospital institutional review board (approval number 21481).

**Results**

**Demographic characteristics of the study patients**

The characteristics of the study patients \((n = 8)\) are shown in Table 1. There were four males and four females, with a median age of 11.5 years (range, 1.8–32 years). Laboratory data were from the time of the last LBx. Percutaneous LBx
was performed 18 times, 18 specimens were obtained from eight patients. A summary of LBx and laboratory values is presented in Table 2. Regarding the degree of liver fibrosis based on histological examination, F0 was observed in three specimens, F1 in 12, and F2 in 3. M2BPGi values in this study ranged from 0.48 to 1.62 COI (median, 0.74 COI). CRP ranged from 0.04 to 0.85 mg/dL. Total bilirubin ranged from 0.2 to 1.5 mg/dL. None of the patients had IFALD.

### M2BPGi and liver fibrosis

By fibrosis stage (F0–F2), the mean M2BPGi value was 0.44 COI (SD, 0.06 COI) in patients with F0 fibrosis, 0.78 COI (SD, 0.39 COI) in patients with F1 fibrosis, and 1.63 COI (SD, 1.16 COI) in patients with F2 fibrosis. The mean M2BPGi value was significantly higher in patients with F2 versus F1 fibrosis \( (P < 0.016) \) and in patients with F2 versus F0 fibrosis \( (P < 0.028) \) (Fig. 1a).

### Other fibrosis markers and liver fibrosis

By fibrosis stage (F0–F2), the mean AST/ALT ratio was 1.36 (SD, 0.54) in patients with F0 fibrosis; 0.87 (SD, 0.27) in patients with F1 fibrosis, and 1.53 (SD, 0.62) in patients with F2 fibrosis. The mean AST/ALT ratio was significantly higher in patients with F2 versus F1 fibrosis \( (P < 0.017) \) (Fig. 1b). However, there was no statistically significant difference between patients with F2 and F0 fibrosis.

By fibrosis stage (F0–F2), mean APRI was 0.44 (SD, 0.10) in patients with F0 fibrosis, 0.61 (SD, 0.37) in patients with F1 fibrosis, and 0.54 (SD, 0.15) in patients with F2 fibrosis. There was no statistically significant difference between the groups (Fig. 1c).

By fibrosis stage (F0–F2), mean FIB-4 index was 0.41 (SD, 0.04) in patients with F0 fibrosis, 0.39 (SD, 0.35) in patients with F1 fibrosis, and 0.90 (SD, 0.16) in patients with F2 fibrosis. Mean FIB-4 index was significantly higher in patients with F2 versus F1 fibrosis \( (P < 0.022) \) (Fig. 1b). However, there was no statistically significant difference between patients with F2 and F0 fibrosis (Fig. 1d).

### M2BPGi and fibrosis stages over times

M2BPGi and fibrosis stage at the first and latest liver biopsies of six patients who underwent liver biopsy more than once were plotted to figure out the progression...
of liver fibrosis in IFALD patients. (Fig. 2) The interval between the first and latest liver biopsy was median 14.2 months (11.0–50.1 months). There was no change in fibrosis stage in five cases during this observation period, and one case changed from F1 to F2. M2BPGi increased in three cases and decreased in three cases.

**ROC curve analysis**

For predicting progressive liver fibrosis (F2), a M2BPGi level of 1.62 COI yielded a high AUC (0.73). For presence of liver fibrosis (≥ F1), an M2BPGi level of 0.44 COI yielded a high AUC (0.89) (Fig. 3a, b).

**Discussion**

The prognosis of persistent IF depends on complications, including IFALD. The prognosis of IF with IFALD is poor [14]. The prognosis of IFALD depends greatly upon the extent of hepatic fibrosis. Patients with advanced liver fibrosis have higher morbidity due to complications from cirrhosis; they also have higher mortality [15]. In ultra-short bowel syndrome, IFALD occurs rapidly and cirrhosis is likely [16]. Patients with IF and IFALD might need combined liver and intestinal transplantation [17]. Early detection of liver fibrosis allows patient consultation at an intestinal rehabilitation and transplant center,

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**Fig. 1** Relationship between fibrosis markers and the stage of fibrosis. Fibrosis stages were described METVIR score. a M2BPGi, b AST/ALT, c APRI, d FIB-4 index. M2BPGi Mac-2 binding protein glycosylation-modified isomer, APRI aspartate aminotransferase to platelet ratio index, FIB-4 fibrosis-4 index.
pre-transplant evaluation, and transplant listing [18]. In Japan, it is necessary to perform isolated intestinal transplantation before IFALD and liver cirrhosis progression because combined transplantation of the liver and small intestines is difficult in Japan due to a shortage of donors.

Therefore, early detection of IFALD in development is important. For this purpose, identifying liver fibrosis progression is essential. However, the development of fibrosis cannot be detected by blood tests until the late stage [19]. LBx is the standard for assessing the degree of liver fibrosis. However, it might cause complications such as organ injury, hemorrhage, and pain. In pediatric patients, general anesthesia is needed for LBx [20]. Serial LBx should be avoided, but it might be needed to follow the progression of fibrosis. Another problem is that the evaluation of fibrosis by LBx is uncertain due to sampling error and variation among observers [21]. LBx provides a classified grading system that allows comparing fibrosis stage among patients. However, LBx allows for the evaluation at a static point. In addition, there are only five classifications (F0–F4) in the METAVIR system. A marker that allows for the identification of patients with IFALD progression, to avoid repeating LBx procedures unnecessarily, is desirable.

In recent years, several noninvasive tests have been developed. Noninvasive biomarkers for predicting fibrosis in patients with IFALD have been explored. APRI is one such biomarker of fibrosis. APRI has been used to detect fibrosis and cirrhosis in adult patients with hepatitis C [11]. In pediatric patients, APRI has been used to evaluate fibrosis progression during follow-up in biliary atresia [22]. APRI > 1.6 in patients with IFALD correlates with advanced fibrosis in the pediatric population [23]. FIB-4 index is another fibrosis marker that has been used in patients with IFALD. FIB-4 index is a biomarker of fibrosis that has been used in patients with IFALD. FIB-4 index and liver fibrosis stage are positively correlated. This evaluation of FIB-4 index versus LBx supports the use of the FIB-4 index in the detection of liver fibrosis in IF [24]. These methods detect high levels of liver fibrosis in IFALD that has already developed. They were inadequate for early detection of liver fibrosis before IFALD has developed. As a
non-blood test–based methods, transient elastography measures the elasticity or stiffness of the liver to detect more severe hepatic fibrosis using ultrasound. Ultrasound-based transient elastography is another less invasive method for evaluating liver fibrosis that has recently been reported as highly useful [25]. Its use in children has been reported [26, 27]. However, there have been no reports about early detection of liver fibrosis prior to the development of IFALD.

These methods detect high levels of liver fibrosis and are inadequate for early detection. M2BPGi is a predictor of liver fibrosis that performed better than other markers such as FIB-4 index. M2BPGi might be the most reliable serum biomarker [5]. M2BPGi is a marker for assessing liver fibrosis in viral hepatitis [5, 6, 9]. In addition, M2BPGi is useful for assessing liver fibrosis in patients with Primary Biliary Cholangitis [28], autoimmune hepatitis [8], and non-alcoholic fatty liver disease [29]. Its usefulness has been demonstrated in pediatric biliary atresia [10]. M2BPGi might be useful for follow-up of fibrosis progression over time even if fibrosis stage remains constant [30].

ROC curve analysis demonstrated that serum M2BPGi levels in patients with IF have good diagnostic ability for detecting grade F2 fibrosis. We found that the degree of liver fibrosis differed by M2BPGi level. Our study suggests that M2BPGi is useful for predicting progressive fibrosis (≥ F2) with a cutoff of 1.62 COI and the presence of liver fibrosis (≥ F1) with a cutoff of 0.44 COI. LBx can be avoided until M2BPGi predicts the presence of liver fibrosis before IFALD in patients without jaundice. The primary strength of our study is the inclusion of a unique cohort of patients who underwent LBx before the development of IFALD. Once patients develop jaundice, IFALD can be easily detected. Utilizing the proposed cutoff values, sensitivity and specificity values are provided for future studies to include or exclude advanced liver fibrosis simply based on M2BPGi.

We acknowledge several study limitations. The primary limitation of our study is the inclusion of only individuals preparing for intestinal transplantation. The study population does not cover all patients with IF. There were not enough patients to produce significant specificity and sensitivity in ROC curve analysis. Additionally, subgroup analysis about the correlation between the M2BPGi value and factors for liver damage could not be performed due to the small number of cases this time. Subgroups will be a primary disease, patients’ age, duration, and composition of PN, length of residual intestine, presence of ileocecal valve, and so on. Further study is required after the accumulation of cases. The progression of liver fibrosis and the increase of M2BPGi were not evident in this study since there was not enough observation period. The relationship between the progress of liver fibrosis and the value of M2BPGi in IF patients are for further investigation. We did not perform elastography; thus, elastography findings could not be compared with M2BPGi data. Further analysis will be needed. Lastly, although M2BPGi is significantly correlated with fibrosis stage, the sensitivity of the M2BPGi index is insufficient. It should be used with other markers such as FIB-4 index before performing LBx to prove liver fibrosis.

In conclusion, serum M2BPGi is a novel marker for liver fibrosis in patients with IF. It is especially useful for follow-up in patients with IF prior to IFALD. Serum M2BPGi levels can support the interpretation of liver status.

Author contributions TU, KB made study conception and design. KT, KD, MK collected data. MN, YT analyzed data. KM, MW, TU drafted the manuscript. HO revisited the manuscript. All authors reviewed the manuscript.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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