

Mac-2-binding protein glycosylation isomer is useful to predict muscle cramps in patients with chronic liver disease

Takao Miwa, MD^{a,b,*} , Tatsunori Hanai, MD, PhD^{a,c}, Yuko Sakai, RD^d, Takahiro Kochi, MD, PhD^b, Naoki Katsumura, MD, PhD^b, and Masahito Shimizu, MD, PhD^a

Abstract

Muscle cramps are frequently overlooked and worsen the quality of life in patients with chronic liver disease (CLD). Therefore, a valuable biomarker for predicting muscle cramps is required in the clinical setting. This study aimed to investigate whether the serum Mac-2-binding protein glycosylation isomer (M2BPGi) levels, a reliable liver fibrosis marker, could predict muscle cramps in patients with CLD. This retrospective study included 80 patients with CLD. Muscle cramps were assessed using a questionnaire regarding their presence, frequency, pain severity, and duration. The associated predictors were analyzed using logistic regression analysis. The diagnostic accuracy and optimal cutoff values were evaluated using receiver operating characteristic curves. Of the 80 patients, 55% had muscle cramps and showed significantly higher serum M2BPGi levels than those without them (4.54 cutoff index [COI] vs 2.20; $P = .001$). Multivariate analysis revealed that M2BPGi (odds ratio [ORs], 1.19; 95% confidence interval, 1.003–1.42; $P = .046$) was independently associated with the presence of muscle cramps. The optimal COI value for predicting muscle cramps was 3.95, and the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 61.4%, 80.6%, 79.4%, 63.0%, and 70.0%, respectively. Patients with a COI value ≥ 3.95 had a 2-fold higher incidence of muscle cramps than patients with a COI value < 3.95 (79% vs 37%; $P < .001$). M2BPGi levels were also associated with the duration of muscle cramps. Serum M2BPGi appears useful as a biomarker for predicting muscle cramps in patients with CLD.

Abbreviations: AUC = area under the receiver operating characteristic curve, CI = confidence interval, CLD = chronic liver disease, COI = cutoff index, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, IQR = interquartile range, M2BPGi = Mac-2-binding protein glycosylation isomer, MELD = model for end-stage liver disease, OR = odds ratio, QOL = quality of life.

Keywords: chronic liver disease, liver cirrhosis, liver fibrosis, Mac-2-binding protein glycosylation isomer, muscle cramps, quality of life

1. Introduction

What worsens the quality of life (QOL) in patients with chronic liver disease (CLD)? This is an important question as patients with CLD life expectancy increased due to recent advances in antivirals and nutritional treatment.^[1,2] Complications of cirrhosis, such as malnutrition, variceal bleeding, and hepatic encephalopathy, can lead to a poor prognosis and decreased QOL for those patients.^[3,4] Recent studies have revealed that muscle cramps also contribute to poor QOL in patients with CLD causing sleep disturbance.^[3,5]

Muscle cramps are painful, visible, and palpable contractions in one or a part of a muscle during rest and sleep. Muscle cramps are associated with various medical pathologies such as chronic heart disease, renal failure, respiratory, endocrine, neurological diseases, cancer, magnesium or calcium deficiency,

and CLD.^[5–8] There is a high prevalence of muscle cramps involving 50% of the patients with CLD.^[5,6] However, muscle cramps are often ignored in clinical settings because clinicians do not observe them until the patient complains. There is no useful examination procedure developed to diagnose muscle cramps. On the other hand, intervention for muscle cramps has been reported to improve QOL in patients with cirrhosis.^[9] Therefore, identifying a muscle cramp biomarker could allow early detection and intervention, thus improving the QOL in patients with CLD.

The mechanisms of muscle cramps in CLD involve nerve dysfunction, energy metabolism changes, electrolyte imbalance, and plasma volume loss.^[10] Several factors, such as older age, female sex, comorbid diabetes, advanced cirrhosis (worse Child-Pugh score, lower platelet count), shifts in plasma volume (hyponatremia), and diuretics use are reported to be predictive of

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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^a Department of Gastroenterology/Internal Medicine, Gifu University Graduate School of Medicine, Gifu, Japan, ^b Department of Gastroenterology, Chuno Kosei Hospital, Seki, Japan, ^c Center for Nutrition Support & Infection Control, Gifu University Hospital, Gifu University Hospital, Gifu, Japan, ^d Department of Nutrition, Chuno Kosei Hospital, Seki, Japan.

*Correspondence: Takao Miwa, Department of Gastroenterology/Internal Medicine, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan (e-mail: miwa_t@gifu-u.ac.jp).

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muscle cramping as a complication of CLD.^[5,9–12] These reports suggest that advanced cirrhosis and liver fibrosis progression seem to have a strong association with muscle cramping. However, it is not clear whether liver fibrosis assessment could contribute to screening for muscle cramps.

The Mac-2-binding protein glycosylation isomer (M2BPGi) is a secreted glycoprotein produced in liver stellate cells and acts as a messenger sent to Kupffer cells during liver fibrosis.^[13,14] M2BPGi has recently been accepted as a reliable liver fibrosis marker.^[13] Measurement of M2BPGi is also useful for predicting clinical outcomes related to cirrhosis, such as the development of hepatocellular carcinoma (HCC),^[15] postoperative liver failure,^[16] and mortality.^[17] However, whether serum M2BPGi levels can predict muscle cramps in CLD remains unknown. The purpose of this study was to examine the predictors of muscle cramps in patients with CLD, especially focusing on serum levels of M2BPGi.

2. Methods

2.1. Study design and patients

This retrospective study included 80 patients with CLD at the Chuno Kosei Hospital (Seki, Japan) between November 2018 and April 2020. The inclusion criteria were patients aged ≥ 20 years, CLD of any etiology, and assessment of muscle cramps. The study protocol was reviewed and approved by the ethics committee of the Chuno Kosei Hospital (approval no. R2-12). Informed consent from the participants was obtained using an opt-out approach because of the study's retrospective nature. This study was performed following the 1964 Declaration of Helsinki.

2.2. Assessment of muscle cramps

Muscle cramps were assessed using a questionnaire based on a previous nationwide survey conducted in Japan.^[5,18] Questions related to muscle cramps included symptoms within the past month, frequency, the severity of pain using a visual analog scale, and duration. The frequency of muscle cramps was assessed as daily, weekly, or monthly, and \geq once a week were assessed as frequent muscle cramps. The severity of pain was assessed using the visual analog scale (0: none, 5: the most severe) and ≥ 4 was assessed as severe pain. The duration of cramps was reported as seconds, minutes, or hours and >1 minute were assessed as long duration. The questionnaire was administered to each patient at the time of nutrition guidance performed by a well-trained dietician. The meaning of each question was explained to the patient by the dietician if the patient required assistance.

2.3. Data collection

The patients' clinical characteristics and laboratory variables were obtained during the muscle cramp assessment. The collected information on medications included branched-chain amino acids, L-carnitine, and diuretics. Serum M2BPGi levels were measured using a fully automated HISCL-2000i Immunoanalyzer (Symex, Hyogo, Japan).^[17] CLD, such as chronic hepatitis and cirrhosis, were diagnosed based on clinical, biochemical, and radiological features. Liver function reserves were assessed using the Child-Pugh classification and model for end-stage liver disease (MELD) score.^[19,20] The FIB-4 index was calculated using the following equation: age (years) \times aspartate aminotransferase (IU/L)/(platelet counts [$10^9/L$]) \times (alanine transaminase [IU/L])^{1/2}.^[21]

2.4. Statistical analyses

Continuous variables are represented as a median and interquartile range (IQR). Categorical variables are expressed as

the number of patients and percentages (%). Baseline patient characteristics were compared using the chi-squared test or the Mann–Whitney *U* test. The correlation of continuous variables was evaluated using Spearman's rank correlation coefficient. Predictors with *P* values $<.05$ in the univariate logistic regression analysis were included in the multivariate analysis. The results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The area under the receiver operating characteristic curve (AUC) was calculated to evaluate the diagnostic accuracy. The optimal cutoff value was estimated using the Youden index, indicating the maximum point in "sensitivity + specificity - 1". The significance threshold was set at *P* $<.05$. Statistical analyses were performed using the JMP 14 software (SAS Institute, Cary, North Carolina) and R-3.5.2 software (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline patient characteristics

A total of 80 participants with CLD (43 with chronic hepatitis and 37 with cirrhosis) were enrolled in this study. Their median age was 70 years, and 63% of the participants were men. CLD was attributed to hepatitis B virus (5%), hepatitis C virus (HCV) (19%), alcohol-related liver disease (36%), and other etiologies (40%). HCC was associated with 53% of patients. The prevalence of Child-Pugh class A, B, and C was 49%, 40%, and 11%, respectively. The median MELD score was 9 (IQR, 8–13) points. The median serum M2BPGi level was 3.47 (IQR, 1.34–6.74 cutoff index [COI]) (Table 1). There was no statistical significance in serum M2BPGi levels between males and females (3.83 vs 2.93 COI; *P* = .21).

3.2. Prevalence, frequency, pain severity, and duration of muscle cramps in patients with CLD

Muscle cramps were observed in 55% of the enrolled patients with CLD (*n* = 44). The prevalence of muscle cramps was 65% in patients with cirrhosis (24/37 patients) and 47% in those with chronic hepatitis (20/43 patients). Among the patients who reported muscle cramps, 61% (*n* = 27) had symptoms more than once a week. In assessing the muscle cramps severity, 41% (*n* = 18) had severe pain (visual analog scale ≥ 4). Regarding the duration of cramps, 62% (*n* = 28) reported long duration (>1 minute). The details of muscle cramps in each etiology are shown in subgroup analysis (see Table S1, <http://links.lww.com/MD/H622>, Supplemental Content 1, which illustrated comparison between etiology of CLD and characteristics of muscle cramps).

3.3. Comparison of baseline characteristics between patients with and without muscle cramps

Patients with muscle cramps showed significantly higher serum M2BPGi levels than those without muscle cramps (4.54 vs 2.20 COI; *P* = .001). Patients with muscle cramps showed more advanced liver disease in terms of platelet count than those without cramps ($111 \times 10^9/L$ vs $155 \times 10^9/L$; *P* = .028). The incidence of HCC was significantly lower in patients with muscle cramps than in those without muscle cramps (39% vs 69%; *P* = .006) (Table 1).

3.4. Association of M2BPGi with liver function reserves and fibrosis markers

The median M2BPGi in Child-Pugh classes A, B, and C were 1.74, 4.42, and 9.51 COI, respectively, and the level was significantly higher in patients with worse Child-Pugh class (*P* $<.001$ for all comparisons; Fig. 1a). As for liver function

Table 1
Baseline characteristics of patients with chronic liver disease.

Characteristic	Total	Muscle Cramps+	Muscle cramps–	P value*
	(n = 80)	(n = 44)	(n = 36)	
Age (yrs)	70 (63–77)	68 (57–76)	74 (64–78)	.11
Male sex, n (%)	50 (63)	25 (57)	25 (70)	.25
BMI (kg/m ²)	24.6 (21.4–26.6)	24.2 (21.1–26.3)	24.9 (22.1–27.5)	.35
Etiology of CLD, n (%)				.51
HBV	4 (5)	3 (7)	1 (3)	
HCV	15 (19)	10 (23)	5 (14)	
ALD	29 (36)	16 (36)	13 (36)	
Others	32 (40)	15 (34)	17 (47)	
Ascites, n (%)	23 (29)	14 (32)	9 (25)	.50
Diabetes, n (%)	38 (48)	17 (38)	21 (58)	.08
HCC, n (%)	42 (53)	17 (39)	25 (69)	.006
Cirrhosis, n (%)	37 (46)	24 (55)	13 (36)	.10
Child-Pugh score	6 (5–9)	7 (5–9)	6 (5–8)	.62
Child-Pugh class (A/B/C)	39/32/9	20/17/7	19/15/2	.34
FIB-4 index	4.26 (3.07–6.73)	4.79 (3.19–8.18)	4.18 (1.89–5.44)	.09
Laboratory test				
MELD score	9 (8–13)	9 (8–13)	9 (7–12)	.51
PT-INR	1.15 (1.05–1.31)	1.12 (1.07–1.37)	1.13 (1.04–1.28)	.10
Platelets (10 ⁹ /L)	124 (80–184)	111 (73–162)	155 (105–216)	.028
Creatinine (mg/dL)	0.77 (0.64–0.96)	0.75 (0.63–0.95)	0.82 (0.69–0.96)	.30
AST (IU/L)	37 (24–52)	40 (27–56)	32 (21–46)	.17
ALT (IU/L)	24 (15–33)	23 (15–33)	24 (16–35)	.99
Albumin (g/dL)	3.3 (2.7–3.8)	3.1 (2.6–3.8)	3.5 (2.9–3.8)	.28
Bilirubin (mg/dL)	1.1 (0.7–1.9)	1.1 (0.8–2.1)	1.0 (0.7–1.6)	.32
Sodium (meq/L)	140 (137–141)	140 (137–141)	140 (137–142)	.62
Zinc (µg/mL)	59 (45–73)	58 (42–71)	62 (52–73)	.23
Ammonia (µg/dL)	67 (49–91)	68 (56–97)	60 (39–87)	.12
M2BPGi (COI)	3.47 (1.34–6.74)	4.54 (2.46–8.11)	2.20 (1.13–3.89)	.001
Medication use				
BCAA, n (%)	30 (38)	17 (39)	13 (36)	.82
L-carnitine, n (%)	16 (20)	12 (27)	4 (11)	.07
Diuretics, n (%)	28 (35)	18 (41)	10 (28)	.22

Values are presented as number (%) or median (interquartile range).

*Statistical analysis was performed using the chi-squared test or Mann–Whitney U test.

ALD = alcoholic liver disease, ALT = alanine transaminase, AST = aspartate aminotransferase, BCAA = branched-chain amino acid, BMI = body mass index, CLD = chronic liver disease, COI = cutoff index, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, M2BPGi = Mac-2 binding protein glycosylation isomer, MELD = model for end-stage liver disease, PT-INR = prothrombin time-international normalized ratio.

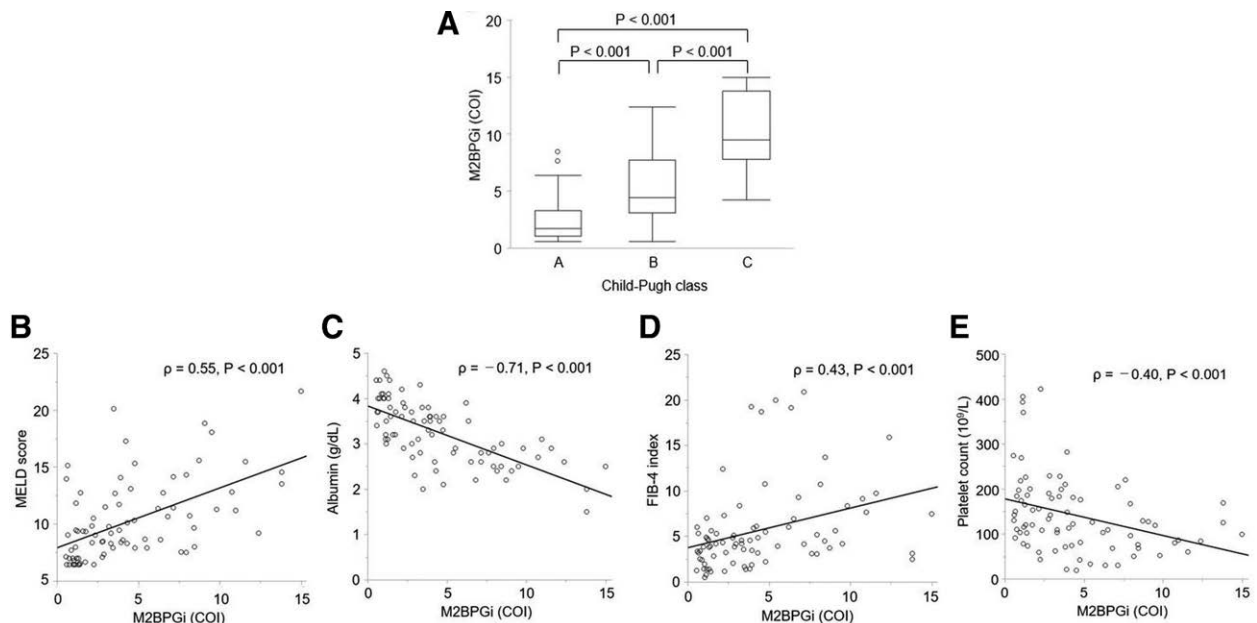


Figure 1. Association of M2BPGi with liver function reserves and fibrosis. (a) Association between serum M2BPGi levels and Child-Pugh score were analyzed using the Mann–Whitney U test. Correlation between serum M2BPGi levels and (b) MELD score, (c) serum albumin levels, (d) FIB-4 index, and (e) platelet count is evaluated using the Spearman’s rank correlation coefficient test. COI = cutoff index, MELD = a model for end-stage liver disease, M2BPGi = Mac-2-binding protein glycosylation isomer.

reserves, serum M2BPGi level positively correlated with the MELD score ($\rho = 0.55$; $P < .001$; Fig. 1b) and negatively correlated with serum albumin level ($\rho = -0.71$; $P < .001$; Fig. 1c). As for fibrosis markers, serum M2BPGi level positively correlated with FIB-4 index ($\rho = 0.43$; $P < .001$; Fig. 1d) and negatively correlated with serum platelet count ($\rho = -0.40$; $P < .002$; Fig. 1e).

3.5. Predictive factors of muscle cramps in patients with CLD

As shown in Table 2, univariate analysis showed that HCC, serum platelet count and M2BPGi levels were significantly associated with muscle cramps. Multivariate analysis showed that HCC complications (OR, 0.19; 95% CI, 0.06–0.60; $P = .004$) and serum M2BPGi levels (OR, 1.19; 95% CI, 1.003–1.42; $P = .046$) were independently associated with muscle cramps in patients with CLD.

To investigate the diagnostic accuracy of serum M2BPGi levels in muscle cramps, the AUC was evaluated. The obtained AUC was 0.71 (95% CI, 0.60–0.83; Fig. 2a), and the optimal cut-off value of serum M2BPGi levels for predicting muscle cramps was 3.95 COI. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for this cutoff were 61.4%, 80.6%, 79.4%, 63.0%, and 70.0%, respectively. Patients with COI value of serum M2BPGi ≥ 3.95 had a significantly higher prevalence of muscle cramps than those with COI value of serum M2BPGi < 3.95 (79% vs 37%; $P < .001$; Fig. 2b).

3.6. Factors related to duration, frequency, and pain severity of muscle cramps in patients with CLD

Comparison between patients with long and short duration of muscle cramps revealed significant differences in the prevalence of diabetes, platelet count, zinc, M2BPGi, FIB-4 index, and diuretics use. Serum M2BPGi levels were significantly higher in patients with prolonged muscle cramps than those with short duration (5.47 vs 3.08 COI; $P = .023$, Table 3). The frequency of muscle cramps was associated with patient's sex and existing HCC complications; however, they were unrelated to serum M2BPGi levels (see Table S2, <http://links.lww.com/MD/H623>, Supplemental Content 2, which illustrated comparison between patients with and without frequent cramps). There were not any significant factors, including M2BPGi levels, related to the pain severity of the muscle cramps (see Table S3, <http://links.lww.com/MD/H624>, Supplemental Content 3, which illustrated comparison between patients with and without severe pain).

4. Discussion

Muscle cramps are a serious complication in patients with CLD.^{15,61} The patients enrolled in the present study showed a high prevalence of muscle cramps (55%), which was similar to findings of previous studies with larger sample sizes (from 49% to 55%).^{19–11,181} Among patients with muscle cramps, 61% experienced them more than once a week, 41% had severe pain, and 62% reported long duration. The present study results again

Table 2

Predictors of muscle cramps in patients with chronic liver disease.

Characteristic	Univariate		Multivariate	
	OR (95% CI)	P value*	OR (95% CI)	P value*
Age (yrs)	0.97 (0.94–1.01)	.13		
Male sex	0.58 (0.23–1.46)	.25		
BMI (kg/m ²)	0.92 (0.83–1.03)	.12		
Etiology of CLD, n (%)				
HBV†	1.00		1.00	
HCV	0.67 (0.05–8.16)	.75	0.30 (0.01–6.70)	.44
ALD	0.41 (0.04–4.43)	.44	0.09 (0.00–1.95)	.12
Others	0.29 (0.03–3.14)	.31	0.13 (0.01–2.78)	.19
Ascites	1.40 (0.52–3.75)	.50		
Diabetes	0.45 (0.18–1.10)	.08		
HCC	0.28 (0.11–0.70)	.007	0.19 (0.06–0.60)	.004
Cirrhosis, n (%)	2.12 (0.86–5.24)	.10		
Child-Pugh score	1.11 (0.89–1.39)	.36		
FIB-4 index	1.06 (0.96–1.18)	.24		
Laboratory test				
MELD score	1.07 (0.94–1.22)	.30		
PT-INR	12.27 (0.83–182.11)	.06		
Platelet (10 ⁹ /L)	0.92 (0.87–0.98)	.005	0.94 (0.87–1.01)	.07
Creatinine (mg/dL)	0.77 (0.27–2.23)	.63		
AST (IU/L)	1.00 (0.97–1.01)	.96		
ALT (IU/L)	1.00 (0.98–1.02)	.91		
Albumin (g/dL)	0.72 (0.37–1.37)	.31		
Bilirubin (mg/dL)	1.23 (0.86–1.75)	.23		
Sodium (meq/L)	1.00 (0.88–1.15)	.96		
Zinc (μg/mL)	0.99 (0.96–1.01)	.22		
Ammonia (μg/dL)	1.00 (0.99–1.02)	.50		
M2BPGi (COI)	1.26 (1.08–1.48)	.001	1.19 (1.003–1.42)	.046
Medication use				
BCAA	1.11 (0.45–2.78)	.82		
L-carnitine	3.00 (0.87–10.30)	.07		
Diuretics, n (%)	1.80 (0.70–4.63)	.22		

*Univariate and multivariate logistic regression analyses are performed to evaluate possible predictors of muscle cramps.

†Reference group.

ALD = alcoholic liver disease, ALT = alanine transaminase, AST = aspartate aminotransferase, BCAA = branched-chain amino acid, BMI = body mass index, CI = confidence interval, CLD = chronic liver disease, COI = cutoff index, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, M2BPGi = Mac-2 binding protein glycosylation isomer, MELD = model for end-stage liver disease, OR = odds ratio, PT-INR = prothrombin time-international normalized ratio.

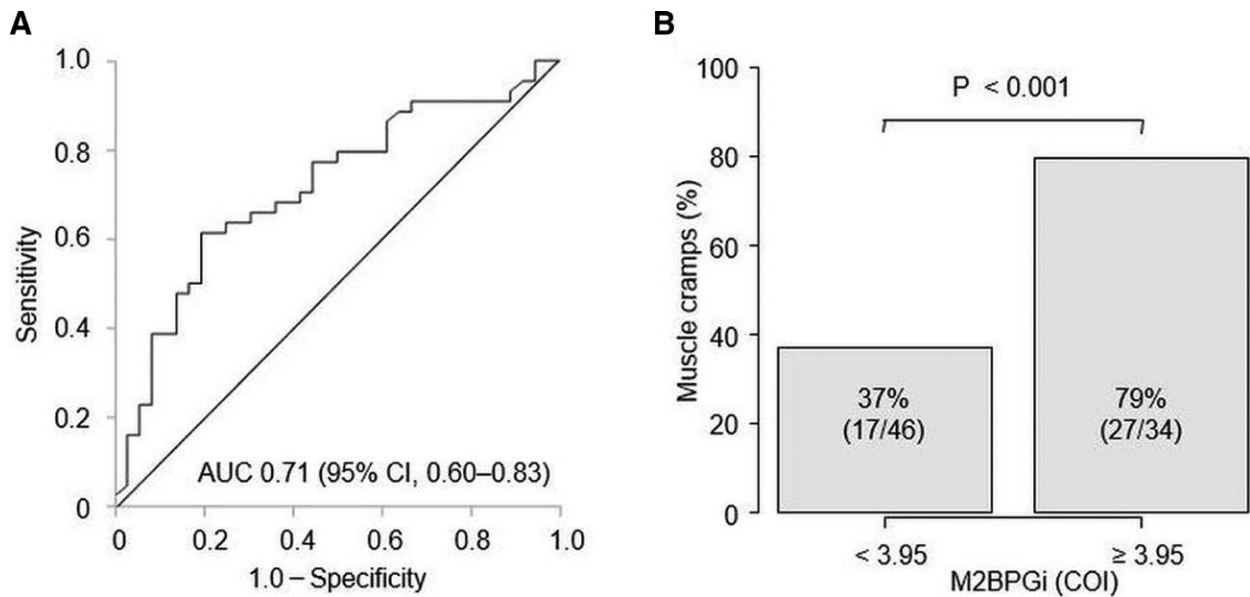


Figure 2. The optimal cutoff value of M2BPGi for predicting muscle cramps in patients with CLD. (a) The receiver operating characteristic curve for M2BPGi in predicting muscle cramps. The AUC is 0.71, which gives a COI value of 3.95 of M2BPGi. (b) Comparison of the frequency of muscle cramps between CLD patients with COI value of serum M2BPGi < 3.95 COI and those with ≥ 3.95. AUC = area under the receiver operating characteristic curve, CI = confidence interval, CLD = chronic liver disease, COI = cutoff index, M2BPGi = Mac-2-binding protein glycosylation isomer.

Table 3
Comparison between patients with long and short duration of muscle cramps.

Characteristic	Long duration (n = 28)	Short duration (n = 52)	P value*
Age (yrs)	69 (59–78)	71 (63–77)	.84
Male sex, n (%)	10 (36)	20 (38)	.81
BMI (kg/m ²)	23.2 (20.7–27.2)	24.8 (22.0–26.2)	.48
Etiology of CLD, n (%)			.10
HBV	3 (11)	1 (2)	
HCV	7 (29)	8 (15)	
ALD	11 (39)	18 (35)	
Others	7 (25)	25 (48)	
Ascites, n (%)	10 (36)	13 (25)	.31
Diabetes, n (%)	8 (29)	30 (58)	.019
HCC, n (%)	13 (46)	29 (56)	.42
Cirrhosis, n (%)	17 (61)	20 (38)	.06
Child-Pugh score	7 (5–9)	6 (5–8)	.27
Child-Pugh class (A/B/C)	12/11/5	27/21/4	.37
FIB-4 index	5.26 (3.35–9.25)	4.17 (2.49–5.80)	.046
Laboratory test			
MELD score	9 (8–13)	9 (7–12)	.31
PT-INR	1.23 (1.07–1.41)	1.14 (1.05–1.30)	.10
Platelet (10 ⁹ /L)	100 (72–140)	145 (102–200)	.030
Creatinine (mg/dL)	0.78 (0.65–0.96)	0.76 (0.64–0.96)	.76
AST (IU/L)	39 (27–58)	34 (22–47)	.29
ALT (IU/L)	23 (16–32)	24 (15–35)	.85
Albumin (g/dL)	3.0 (2.6–3.8)	3.5 (2.9–3.8)	.14
Bilirubin (mg/dL)	1.1 (0.9–2.1)	1.1 (0.7–1.8)	.52
Sodium (meq/L)	139 (137–140)	140 (137–142)	.31
Zinc (µg/mL)	50 (36–67)	65 (51–78)	.019
Ammonia (µg/dL)	68 (56–89)	66 (44–91)	.42
M2BPGi (COI)	5.47 (2.46–8.11)	3.08 (1.17–4.70)	.023
Medication use			
BCAA, n (%)	13 (46)	17 (33)	.23
L-carnitine, n (%)	8 (29)	8 (15)	.16
Diuretics, n (%)	15 (54)	13 (25)	.015

Values are presented as a number (%) or median (interquartile range).

*Statistical analysis is performed using the chi-squared test or Mann–Whitney U test.

ALD = alcoholic liver disease, ALT = alanine transaminase, AST = aspartate aminotransferase, BCAA = branched-chain amino acid, BMI = body mass index, CLD = chronic liver disease, COI = cut-off index, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, M2BPGi = Mac-2 binding protein glycosylation isomer, MELD = model for end-stage liver disease, PT-INR = prothrombin time-international normalized ratio.

highlight that many patients with CLD suffer from muscle cramps in a clinical setting.

One of the significant findings clearly determined in the present study for the first time is that the value of serum M2BPGi enables the prediction of muscle cramps in patients with CLD. Muscle cramps were more frequent in patients with higher serum M2BPGi levels. In addition, serum M2BPGi levels were significantly higher in patients who reported long durations of cramps. Factors associated with advanced cirrhosis and fibrosis progression have been reported to be strongly involved in the incidence of muscle cramps.^[5,9–12] Therefore, accurate assessment of liver fibrosis might contribute to muscle cramps screening. Monitoring serum M2BPGi levels, a reliable fibrosis marker, is considered to be useful for this purpose. In the present study, M2BPGi levels showed a good correlation with other fibrosis markers, such as the platelet count and FIB-4 index. Moreover, the diagnostic efficacy of M2BPGi in muscle cramps assessment was superior to that of the FIB-4 index. The results of this study suggest that serum M2BPGi might be an accurate biomarker of muscle cramps in addition to liver fibrosis in patients with CLD.

Serum M2BPGi levels have been reported to increase significantly with the progression of liver fibrosis, especially in HCV infection. For instance, the mean COI values of M2BPGi in histological fibrosis stages 1, 2, 3, and 4 were 1.26, 1.81, 4.03, and 7.86, respectively, in HCV-positive patients.^[22] A mean COI value of 3.85 of M2BPGi has also been reported in patients with histological fibrosis stage 2.^[23] Therefore, the COI value of 3.95, which was found to be the optimal cutoff value in predicting muscle cramps in patients with CLD in the present study, might be indicative of histological fibrosis stages 2 to 3. This cutoff value might be reasonable in screening high-risk patients for developing muscle cramps because cirrhotic patients with a COI value ≥ 3.95 of serum M2BPGi had a 2-fold higher prevalence of muscle cramps than those with a COI value < 3.95 . This cutoff value is even more significant clinically, as COI value ≥ 4.0 of M2BPGi, has been considered as a predictor of HCC development.^[24]

In addition to fibrosis, malnutrition results in various complications in patients with cirrhosis, including muscle cramps.^[2,25] Decreased taurine concentrations, carnitine deficiency, and shifts in plasma volume (hypoalbuminemia), all of which are associated with malnutrition, are reported to aggravate muscle cramping in CLD.^[10,12,18,26,27] Liver fibrosis markers might be useful for predicting malnutrition in CLD because liver fibrosis correlates with nutritional status. Indeed, M2BPGi is reported to be significantly associated with nutritional markers such as serum albumin and branched-chain amino acid-to-tyrosine ratio.^[28] In the present study, serum M2BPGi levels significantly correlated with the Child-Pugh class, MELD score, and serum albumin levels, which are commonly used to assess malnutrition and the functional liver reserves in patients with CLD.^[19,20] M2BPGi is shown to reflect nutritional status in CLD and, therefore, might be effective in predicting muscle cramps.^[15]

In the present study, patients with HCC had a significantly lower prevalence of muscle cramps than those without HCC; however, previous Japanese nationwide studies with larger sample sizes have shown no relationship between the presence of HCC and muscle cramps.^[5,18] The results of the present study might be due to selection bias of the study population admitted to our hospital because the patients with HCC, who were planned to receive intensive treatment, had better liver functional reserves (Child-Pugh class [$P = .03$]) compared to those without HCC. This is one of the limitations of the present study.

The present study had other limitations. First, this was a retrospective, single-center study with a small sample size, and we could not exclude bias and unmeasured confounding factors that affected muscle cramps in patients with cirrhosis. Second, sex difference and etiology of CLD may affect the results of our study. In fact, serum M2BPGi levels were significantly higher in patients with muscle cramps than

those without muscle cramps (4.31 vs 1.17 COI; $P = .006$) in patients with non-viral and non-alcohol etiology, however, the statistical power was weak in patients with viral hepatitis (5.41 vs 2.62 COI; $P = .63$) and alcohol-related liver disease (5.97 vs 3.82 COI; $P = .15$) in the present study. A recent large study has shown that the prevalence of muscle cramps has no association with the etiology of CLD.^[5] However, alcohol-related liver disease may require attention because of the effect of alcohol on muscles and nerves.^[29] Third, since muscle cramps are subjective findings, quantification of muscle cramps is difficult in our study. Further prospective studies with larger sample size are required to confirm and validate the results of our research.

It should be emphasized again that muscle cramps are difficult to evaluate objectively. Still, their presence is closely associated with a poor QOL in CLD patients.^[5,9] Therefore, accurate and straightforward biomarkers are needed to identify patients at a high risk of presenting with muscle cramps among patients with CLD. The intriguing finding of the present study is that serum M2BPGi level has the advantage of predicting muscle cramps in patients with CLD after adjusting for the etiology of CLD and using the liver fibrosis markers. M2BPGi might predict muscle cramps in addition to other cirrhosis-related clinical outcomes, such as HCC development and mortality.^[15,17] In addition, M2BPGi might be able to assess the risk of muscle cramps independent of liver fibrosis progression, especially in CLD patients of various etiologies with relatively preserved liver functional reserves, but this possibility needs further investigation.

In conclusion, M2BPGi, a noninvasive liver fibrosis marker, might be a useful biomarker for screening muscle cramps in patients with CLD. The present study's findings have meaningful clinical implications because muscle cramps are frequently overlooked in clinical settings, and little is known about the biomarkers in estimating the presence of muscle cramps in patients with CLD.

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Author contributions

Conceptualization: Takao Miwa, Yuko Sakai.

Data curation: Takao Miwa, Yuko Sakai, Takahiro Kochi, Naoki Katsumura.

Formal analysis: Takao Miwa.

Investigation: Takao Miwa.

Methodology: Takao Miwa, Yuko Sakai.

Project administration: Takao Miwa.

Software: Takao Miwa.

Supervision: Tatsunori Hanai, Takahiro Kochi, Naoki Katsumura, Masahito Shimizu.

Validation: Takao Miwa, Tatsunori Hanai, Yuko Sakai.

Visualization: Takao Miwa.

Writing – original draft: Takao Miwa, Yuko Sakai.

Writing – review & editing: Tatsunori Hanai, Takahiro Kochi, Naoki Katsumura, Masahito Shimizu.

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