Relationship between skeletal muscle mass and liver fibrosis markers for patients with hepatitis C virus related liver disease

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Abstract

We aimed to elucidate the relationship between serum liver fibrosis markers (Mac-2 binding protein glycosylation isomer (M2BPGi), FIB-4 index, aspartate aminotransferase to platelet ratio index and hyaluronic acid), and skeletal muscle mass and to investigate factors linked to skeletal muscle mass loss (SMML) in patients with chronic hepatitis C (CHC, n=277, median age=64 years). We defined patients with psoas muscle index (PMI, sum of bilateral psoas muscle mass calculated by manual trace method at the lumbar level on the computed tomography images) < 27.7 cm²/m² as those with SMML based on the recommendations in current guidelines. Receiver operating curve (ROC) analysis was performed for predicting SMML in 4 liver fibrosis markers and parameters linked to SMML were also investigated in the univariate and multivariate analyses. In terms of liver fibrosis stages, F4 was observed in 115 patients, F3 in 67, F2 in 38, F1 in 53, and F0 in 4. The median (range) PMI for male and female were 6.198 (2.999–13.698) and 4.100 (1.691–7.052) cm²/m², respectively. There were 72 male patients with SMML (55.4%) and 58 female patients with SMML (39.5%) (P=0.0112). In both male and female, a significant inverse correlation between PMI and levels of liver fibrosis markers was observed in all liver fibrosis markers. ROC analyses for predicting SMML revealed that FIB-4 index had the highest area under the ROC (AUC=0.712), followed by M2BPGi (AUC=0.692). In the multivariate analysis of factors linked to SMML, gender (P=0.0003), body mass index (P<0.0001), FIB-4 index (P=0.0039), and M2BPGi (P=0.0121) were found to be significant predictors. In conclusion, liver fibrosis markers, especially FIB-4 index, can be helpful for predicting SMML in CHC patients.

Abbreviations: ALT = alanine aminotransferase, APRI = AST to platelet ratio index, AST = aspartate aminotransferase, AUC = area under the ROC, BMI = body mass index, CHB = chronic hepatitis B, CHC = chronic hepatitis C, CT = computed tomography, DAA = direct-acting antiviral, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, LC = liver cirrhosis, M2BPGi = Mac-2 binding protein glycosylation isomer, NAFLD = nonalcoholic fatty liver disease, NASH = non-alcoholic steatohepatitis, PEM = protein energy malnutrition, PMI = psoas muscle index, ROC = receiver operating characteristic curve, SMML = skeletal muscle mass loss, SVR = sustained virological response.

Keywords: chronic hepatitis C, liver fibrosis marker, predictive ability, skeletal muscle mass loss

1. Introduction

Persistent chronic hepatitis C (CHC) virus infection is associated with liver fibrosis progression[1–3]. In our country, hepatitis C virus (HCV) infection is leading cause of liver cirrhosis (LC), its related complications, and development of hepatocellular carcinoma (HCC).[4] The severity of liver fibrosis is the main determinant of long-term outcomes, driving both liver-related and extrahepatic complications and mortality.[5] Thus, assessing the degree of liver fibrosis correctly plays a significant role for the control of disease progression and for making the therapeutic strategies and evaluating the prognosis for patients with HCV infection.[6,7]

Skeletal muscle is considered to have a role to maintain energy metabolism and nutritional condition and the decrease of skeletal muscle mass may be a considerable impairment condition.[6,7] Although aging can cause skeletal muscle mass loss (SMML), LC is frequently associated with this muscular abnormality.[6,9] Recent studies have demonstrated the role of quantitative muscle assessment in LC patients as a useful marker for reflecting malnutrition and liver function and for predicting prognosis.[10,11] In our previous study, the prevalence of SMML as determined by bioimpedance analysis in LC patients was significantly higher than that in patients with chronic hepatitis without LC.[12] In addition, a recent study demonstrated that sarcopenia as defined by muscle mass loss and a decrease in muscle strength can be a useful predictor for the presence of minimal hepatic encephalopathy.[13]
Various serum liver fibrosis markers for predicting the degree of liver fibrosis have been proposed and validated in recent years as well as radiological assessing methods for liver fibrosis. Of these, FIB-4 index and aspartate aminotransferase (AST) to platelet ratio index (APRI) have been most frequently used liver fibrosis markers in CHC patients. Further, Mac-2 binding protein glycosylation isomer (M2BPGi) was recently established as a novel liver fibrosis glycosobiomarker in patients with HCV-related chronic liver injury with a unique fibrosis-related glycoalteration and speedy bedside testing method. Recent studies reported that M2BPGi level was closely associated with clinical outcomes for patients with chronic hepatitis B (CHB), CHC, autoimmune hepatitis, primary biliary cirrhosis, LC, and HCC. In view of these reports, a hypothesis that liver fibrosis marker level is linked to the SMML in patients with chronic liver diseases can be reached. Indeed, several studies demonstrated that the prevalence of SMML presented a linear increase with the severity of fibrosis in patients with nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH).

However, an extensive literature search has not demonstrated the relationship between skeletal muscle mass and the liver fibrosis markers in CHC patients and these issues need to be clarified. In the current study, we aimed to elucidate the relationship between serum liver fibrosis markers (M2BPGi, FIB-4 index, APRI, and hyaluronic acid) and skeletal muscle mass and to investigate factors linked to the presence of SMML.

2. Patients and methods

2.1. Patients

Between January 2006 and July 2015, a total of 386 individuals with HCV-related liver injury with available stored sera for testing M2BPGi level were admitted to the Division of Hepatobiliary and Pancreatic disease, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan. In this analysis, M2BPGi was tested by using stored sera for all patients. Subjects with HCV-related liver disease are defined as those with HCV antibody positive and hepatitis B surface antigen negative. All subjects underwent liver biopsy. We assessed skeletal muscle mass by employing psoas muscle index (PMI) on the computed tomography (CT) images at baseline. PMI indicates total value of bilateral psoas muscle mass calculated by manual trace method at the lumbar 3 level on the CT images divided by height squared (cm²/m²).

Of these 386 patients, a total of 277 patients had available data for PMI on the CT images and they were analyzed in our previous study and the degree of liver fibrosis have been proposed and validated in recent years as well as radiological assessing methods for liver fibrosis. The median (range) PMI in male patients with F3 (n = 277) was 4.263 cm²/m² (1.790 – 13.698 cm²/m²), while that in female patients (n = 277) was 3.841 cm²/m² (1.691 – 7.052 cm²/m²), respectively. In this analysis, there were 72 male patients with SMML (55.4%) and 58 female patients with SMML (39.5%) as those with SMML based on the recommendations in current guidelines.

The ethics committee meeting of our hospital approved this study protocol and our study protocol adhered to all of the regulations of the Declaration of Helsinki. Informed written consent was obtained from all subjects before liver biopsy.

2.2. Measurement of M2BPGi, HCV-RNA and HCV genotype, and liver histological findings

Serum M2BPGi level was measured as described previously utilizing stored serum samples collected at baseline and it was tested according to a lectin-antibody sandwich immunoassay using the fully automatic immunooanalyser, HISCL-2000i (Sysmex Co., Hyogo, Japan). HCV-RNA concentrations were measured as described previously. HCV genotype was determined by using an HCV Genotype Primer Kit (Institute of Immunology, Tokyo, Japan). Our liver biopsy protocols were explained in our previous study and the degree of liver fibrosis and inflammation was determined as described elsewhere.

2.3. Statistical analysis

Receiver operating characteristic curve (ROC) analysis was performed for calculating the area under the ROC (AUC) for serum M2BPGi, FIB-4 index, APRI, and hyaluronic acid for selecting the optimal cutoff value that maximized the sum of sensitivity and specificity for the presence of SMML. In continuous parameters, the statistical analysis between groups was performed using Student t test, Mann–Whitney U test, or Spearman rank correlation coefficient rs as appropriate. Parameters with P value < .05 in the univariate analysis were entered into the multivariate analysis utilizing the logistic regression analysis. P values of less than .05 were considered to suggest significance. Data are presented as median value (range) unless otherwise mentioned. Statistical analysis was performed with the JMP 11 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the analyzed subjects (n = 277) are summarized in Table 1. There are 130 males and 147 females with the median (range) age of 64 (23–87) years. In terms of liver fibrosis stages, F4 was observed in 115 patients, F3 in 67, F2 in 38, F1 in 53, and F0 in 4. In terms of liver inflammation stages, A3 was observed in 16 patients, A2 in 159, A1 in 100, and A0 in 2. Patients were predominantly HCV genotype 1b (78.7%, 218/277) and higher HCV viral load of ≥5 log IU/mL (85.6%, 237/277). The median (range) PMI for male and female were 6.198 (2.999 – 13.698) and 4.100 (1.691 – 7.052) cm²/m², respectively.

In this analysis, there were 72 male patients with SMML (53.4%) and 58 female patients with SMML (39.5%) (P = .0112).

3.2. The prevalence of SMML according to liver fibrosis stages and inflammation stages

The median (range) PMI in male patients with F4 (n = 55) was 5.909 cm²/m² (2.999 – 9.980 cm²/m²), while that in female patients with F4 (n = 60) was 3.841 cm²/m² (1.691 – 7.032 cm²/m²). The median (range) PMI in male patients with F3 (n = 35) was 6.097 cm²/m² (3.499 – 13.698 cm²/m²), while that in female patients with F3 (n = 32) was 4.034 cm²/m² (2.996 – 6.874 cm²/m²). The median (range) PMI in male patients with F0–2 (n = 40) was 6.627 cm²/m² (4.035 – 13.539 cm²/m²), while that in female patients with F0–2 (n = 55) was 4.263 cm²/m² (1.790 – 6.065 cm²/m²). Thus,
the stepwise decrease in PMI values was observed as the liver fibrotic stage progressed in both male and female. Prevalence of SMML in patients with F4 was significantly higher than that with F0–3 [59.13% (68/115) vs 38.27% (62/162), \( P = .0007 \)] (Fig. 1A). Prevalence of SMML in patients with F3 or more was significantly higher than that with F0–2 [54.95% (100/182) vs 31.58% (30/95), \( P = .0002 \)] (Fig. 1B). Prevalence of SMML in patients with F3 was significantly higher than that with F0–2 [47.76% (32/67) vs 31.58% (30/95), \( P = .0487 \)] (Fig. 1C). The median (range) PMI in male patients with A2 or more (\( n = 84 \)) was 6.153 cm²/m² (2.999–11.014 cm²/m²), while that in female patients with A2 or more (\( n = 91 \)) was 4.057 cm²/m² (1.691–7.052 cm²/m²). Prevalence of SMML in patients with A2 or more was not significantly higher than that with A0 or A1, although the tendency for significance was observed [50.86% (89/175) vs 40.2% (41/102), \( P = .1047 \)] (Fig. 1D).

3.3. ROC analysis for predicting SMML in 4 liver fibrosis markers

ROC analyses for predicting SMML revealed that FIB-4 index had the highest AUC (AUC = 0.712, cutoff point = 3.22, sensitivity = 73.08%, specificity = 62.59%), followed by M2BPGi (AUC = 0.692, cutoff point = 2.03 cutoff index, sensitivity = 79.23%, specificity = 54.42%) (Fig. 2A–D and Table 2).

Table 1
Baseline characteristics (n = 277).

| Variables                  | Number or median (range) |
|----------------------------|--------------------------|
| Age, y                     | 64 (23–87)               |
| Gender, male/female        | 130/147                  |
| PMI, cm²/m², male          | 6.198 (2.999–13.698)     |
| PMI, cm²/m², female        | 4.100 (1.691–7.052)      |
| BMI, kg/m²                 | 22.43 (15.07–37.16)      |
| HCV genotype, 1b/2a/2b/others | 218/37/48               |
| HCV viral load ≥5 log IU/mL | 1/0/0                    |
| AST, IU/L                  | 46 (14–343)              |
| ALT, IU/L                  | 40 (8–396)               |
| ALP, IU/L                  | 254 (58–985)             |
| GGT, IU/L                  | 37 (7–869)               |
| Serum albumin, g/dL        | 4.0 (2.5–4.9)            |
| Total bilirubin, mg/dL     | 0.8 (0.2–2.0)            |
| Prothrombin time (%)       | 87.2 (48.1–121.6)        |
| Platelet count, ×10³/mm³   | 12.9 (3.5–38.7)          |
| Total cholesterol, mg/dL   | 160 (80–278)             |
| M2BPGi (cutoff index)      | 2.88 (0.34–20.0)         |
| FIB-4 index                | 3.39 (0.40–16.52)        |
| APRI                       | 1.068 (0.139–7.372)      |
| Hyaluronic acid, ng/mL     | 122 (9–1420)             |
| Histological findings      |                          |
| F stage, 0/1/2/3/4         |                          |
| A stage, 0/1/2/3           |                          |

3.5. Statistical analysis

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3.4. Relationship between liver fibrosis markers and PMI for male and female

For male, in terms of relationship between liver fibrosis markers and PMI, FIB-4 index had the strongest rs value (rs = -0.4684, P < .0001), followed by M2BPGi (rs = -0.3408, P = .0001) (Fig. 3A–D). For female, in terms of relationship between liver fibrosis markers and PMI, FIB-4 index also had the strongest rs value (rs = -0.3548, P < .0001), followed by APRI (rs = -0.3329, P < .0001) and M2BPGi (rs = -0.3188, P = .0001) (Fig. 4A–D).

3.5. Univariate and multivariate analyses of factors contributing to the presence of SMML

Significant variables linked to the presence of SMML in the univariate analyses are age (P = .0009); gender (P = .0112); body mass index (BMI) (P < .0001); serum albumin (P = .0009); prothrombin time (P = .0027); platelet count (P < .0001); AST (P < .0001); ALT (P = .0277); gamma glutamyl transpeptidase (P = .0054); total cholesterol (P = .0113); M2BPGi (P < .0001); FIB-4 index (P < .0001); APRI (P < .0001); and hyaluronic acid (P < .0001) (Table 3). As FIB-4 index includes age, platelet count, AST, and ALT, they were not entered into the multivariate analysis to avoid the effect of collinearity. The hazard ratios and 95% confidence intervals calculated by using multivariate analysis for the 10 significant parameters (P < .05) in the univariate analysis are presented in Table 4. Gender (P = .0003), BMI (P < .0001), M2BPGi (P = .0121), and FIB-4 index (P = .0039) were found to be independent predictors associated with the presence of SMML (Table 4).

3.6. Levels of liver fibrosis markers in LC patients stratified by the presence of SMML

In LC patients (n = 115), FIB-4 index in the SMML group was significantly higher than that in the non-SMML group (P = .0017), while other liver fibrosis markers were not (Table 5).

3.7. Levels of liver fibrosis markers in non-LC patients stratified by the presence of SMML

In the non-LC patients (n = 162), FIB-4 index (P = .0003), M2BPGi (P < .0001), and APRI (P = .0030) in the SMML group were significantly higher than that in the non-SMML group, while hyaluronic acid was not (Table 5).

| Table 2 | ROC analysis for predicting SMML in four liver fibrosis markers. |
|---------|---------------------------------------------------------------|
|         | M2BPGi | FIB-4 index | APRI | Hyaluronic acid |
| AUC     | 0.692  | 0.712       | 0.688| 0.648          |
| Cutoff point | 2.03  | 3.22        | 1.002 | 187 ng/mL       |
| Sensitivity (%) | 79.23 | 73.08       | 67.69 | 46.92        |
| Specificity (%) | 54.42 | 62.59       | 63.95 | 76.19        |

APRI = AST to platelet ratio index, AUC = area under the receiver operating characteristic curve, COI = cutoff index, M2BPGi = Mac-2 binding protein glycosylation isomer.
4. Discussion

To the best of our knowledge, this is the first report linking SMML with liver damage in CHC in a Japanese population. As levels of liver fibrosis markers can differ in different etiologies of liver diseases even in the same degree of liver fibrosis, we examined the relationship between SMML and levels of liver fibrosis markers in limited patients with CHC. SMLL in liver diseases can occur due to the following mechanisms: aging-induced disruption of the balance between protein synthesis and breakdown in skeletal muscle; and protein energy malnutrition (PEM). Its incidence is high in LC patients because the liver is the primary organ for energy metabolism. Reduced glycogen storage in the cirrhotic liver can accelerate the skeletal muscle degradation by requiring skeletal muscle to

Figure 3. Relationship between liver fibrosis markers and PMI for male. (A) M2BPGi. (B) FIB-4 index. (C) APRI. (D) Hyaluronic acid.

Figure 4. Relationship between liver fibrosis markers and PMI for female. (A) M2BPGi. (B) FIB-4 index. (C) APRI. (D) Hyaluronic acid.
supply glucose and amino acids; the imbalance of protein synthesis related to cytokine signals in the liver and muscle. [11,13,40-42] In our previous investigation, the proportion of PEM in LC patients was significantly higher than that in non-LC patients. [43] In addition, aging also can accelerate liver fibrosis progression. [44] Our current results may be associated with these characteristics in chronic liver diseases.

In our results, the stepwise decrease in PMI was observed with the liver fibrosis progression in both male and female. In particular, we found an inverse correlation between SMML and severity of hepatic fibrosis, also confirmed in non-LC patients. A recent Korean study (n = 309) showed that the prevalence of SMML was well stratified among patients without NAFLD, those with NAFLD, and those with NASH, which were in agreement with our data. [43] In addition, our multivariate analysis revealed that FIB-4 index (P = .0039) and M2BPGI (P = .0121) were found to be significant factors linked to the presence of SMML. These results denote that serum liver fibrosis markers, especially FIB-4 index, can be helpful for predicting SMML. CHC therapy has dramatically changed with the recent accessibility of direct-acting antivirals (DAAs) [47,48] and in our unpublished data, in CHC patients who achieved sustained virological response (SVR) treated by DAAs, levels of liver fibrosis markers significantly improved as compared with pretreatment data. In view of these, skeletal muscle mass can be improved in CHC patients with SVR along with the improvement in liver fibrosis markers. However, further examinations will be needed to confirm these results.

Among 4 variables, FIB-4 index had the strongest risk values in terms of relationship with PMI in both male and female. Further, FIB-4 index had the highest AUC (0.712) for predicting SMML. One possible reason for these results is that FIB-4 index includes age, which is closely associated with the development of SMML. [12,20-24,46] In our previous investigation for predicting liver carcinogenesis in CHB patients treated with entecavir, FIB-4 index rather than APRI had higher predictive ability on carcinogenesis. [47] Liver carcinogenesis can be linked to aging. [47] Although LC-related muscle mass loss can be regarded as secondary sarcopenia, SMML in CLDs can be partly attributed to aging. [47] As aging in Japanese CHC patients has been prominent in recent years, the clinical significance of this liver fibrosis marker may be more pronounced in the future. [44] On the contrary, M2BPGI is a novel liver fibrosis marker that was developed in Japan. [21-23] In our previous study, we demonstrated that this marker is linked to not only liver fibrosis stages but also liver inflammation activity stages and systemic inflammation as reflected by serum high C reactive protein level and serum interferon gamma inducible protein-10 level. [32,48,49] Chronic persistent inflammation can cause muscle mass depletion. [50] Prevalence of SMML in patients with A2 or more tended to be significantly higher than that with A0 or A1 and M2BPGI level in patients with A2 or more was significantly higher than that in patients with A0 or A1 in this study (P < .0001, data not shown).

Our results that M2BPGI was an independent predictor for SMML may be attributed to its close relationship with both liver fibrosis and inflammation.

In our data, lower BMI was an independent adverse predictor for SMML, while in the Korean national study with large

### Table 5

**Comparison of levels of liver fibrosis markers between patients with and without skeletal muscle mass loss (SMML) according to LC status.**

| LC patients (n = 115) | SMML | Non-SMML |
|----------------------|------|----------|
| M2BPGI               | 5.72 (1.06–19.95) | 4.38 (1.28–17.55) |
| FIB-4 index          | 5.20 (0.86–16.13) | 3.94 (1.21–9.35) |
| APRI                 | 1.716 (0.321–5.471) | 1.232 (0.243–7.372) |
| Hyaluronic acid      | 220 (22–1260) | 166 (57–699) |
| **P**               | .0863 | .0017    |

| Non-LC patients (n = 162) | SMML | Non-SMML |
|--------------------------|------|----------|
| M2BPGI                   | 2.83 (0.34–18.77) | 1.38 (0.46–20.0) |
| FIB-4 index              | 3.49 (0.89–16.52) | 2.27 (0.40–12.55) |
| APRI                     | 1.204 (0.217–4.834) | 0.668 (0.139–6.983) |
| Hyaluronic acid          | 106 (16–603) | 70 (9–1420) |
| **P**                    | .2457 | .0001    |

APRI = AST to platelet ratio index, LC = liver cirrhosis, M2BPGI = Mac-2 binding protein glycosylation isomer.
NAFLD cohort (n = 2761), the proportion of SMML was significantly higher in patients with higher BMI. The average BMIs in our cohort and their cohort were 22.9 and 25.8 kg/m², respectively. In our cohort, 66 patients (23.8%) had BMI > 25 kg/m² and only 6 patients (2.2%) had BMI > 30 kg/m². The difference of BMI in baseline characteristics between these studies as well as the difference in liver disease etiologies can cause such different results.

There are several limitations to our study. First, this is a retrospective single-center Japanese study. Thus, whether our data can be adapted to other ethnic populations remains uncertain. Second, the cross-sectional nature of our study makes it impossible to interpret any cause–effect relationship; in other words, an in-depth mechanism for the independent association between the SMML and fibrotic change in the liver was not elucidated in this study. Third, liver biopsy can lead to sampling errors for evaluating the severity of liver fibrosis. Fourth, in this study, psoas muscle mass on the CT images was calculated by manual trace method, not by dedicated computer software. This can cause over- or underestimation of true muscle mass, potentially leading to bias. Finally, there were very few patients with ascites or Child–Pugh B or C in this study. When sufficient number of such patients was included into analysis, interpretation for results may be altered. Our results therefore require to be cautiously interpreted. However, our current results presented that liver fibrosis markers can be useful for predicting SMML in CHC patients. The utility of FIB-4 index and M2BPGi for SMML was confirmed in this analysis. Considering our data for optimal cutoff points for the presence of SMML, in CHC patients with FIB-4 index > 3.22 and/or M2BPGi > 2.03 COI, caution for the presence of SMML should be particularly exercised.

In conclusion, data for serum liver fibrosis markers can provide useful information for predicting SMML in patients with CHC.

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