World Journal of

Hepatology

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ABOUT COVER

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AIMS AND SCOPE

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ORIGINAL ARTICLE

Observational Study

Pre-sarcopenia and Mac-2 binding protein glycosylation isomer as predictors of recurrence and prognosis of early-stage hepatocellular carcinoma

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Abstract

BACKGROUND
The Mac-2 binding protein glycosylation isomer (M2BPGi), a fibrosis marker in various liver diseases, is reportedly a prognostic marker in patients with hepatocellular carcinoma (HCC) who underwent hepatectomy.

AIM
To evaluate whether the M2BPGi value, M2BP, and pre-sarcopenia before radiofrequency ablation (RFA) could be useful recurrence and prognostic markers in patients with early-stage HCC.

METHODS
In total, 160 patients with early-stage primary HCC treated with RFA were separately analyzed as hepatitis C virus (HCV)-positive and HCV-negative. Factors contributing to recurrence and liver-related death, including M2BP, M2BPGi, and skeletal muscle mass index, were statistically analyzed. Eighty-three patients were HCV-positive and 77 were HCV-negative.

RESULTS
In HCV-positive patients, only des-γ-carboxy-prothrombin ≥ 23 mAU/mL was a significant poor prognostic factor affecting survival after RFA. In HCV-negative patients, M2BPGi ≥ 1.86 cutoff index was significantly associated with tumor recurrence, while M2BP was not. M2BPGi ≥ 1.86 cutoff index (hazard ratio, 4.89; 95% confidence interval: 1.97-12.18; *P* < 0.001) and pre-sarcopenia (hazard ratio,

3.34, 95% confidence interval: 1.19-9.37; *P* = 0.022) were independent significant poor prognostic factors in HCV-negative patients.

CONCLUSION
In HCV-negative patients with primary HCC treated with RFA, lower M2BPGi contributed to a lower tumor recurrence rate and longer survival period. Pre-sarcopenia contributed to the poor prognosis independently in HCV-negative patients. These factors might be useful recurrence and prognostic markers for early-stage primary HCC.

Key Words: Mac-2 binding protein; Mac-2 binding protein glycosylation isomer; Pre-sarcopenia; Primary hepatocellular carcinoma; Radiofrequency ablation

Core Tip: Hepatocellular carcinoma (HCC) is prone to recurrence, even if cured at an early stage. Pre-sarcopenia is a poor prognostic factor in the elderly population. The usefulness of the Mac-2 binding protein glycosylation isomer (M2BPGi) to treat HCC has recently attracted attention. In this study, we investigated the recurrence and prognostic factors in patients who underwent radiofrequency ablation for early-stage HCC. Based on our data, pre-sarcopenia and higher M2BPGi, but not M2BP, were useful predictors of the recurrence and poor prognosis of early-stage primary HCC in hepatitis C virus-negative patients.

INTRODUCTION

Hepatocellular carcinoma (HCC) is an important health problem affecting approximately 900000 new cancer cases worldwide. In 2020, > 800000 people died from HCC, accounting for approximately 8.3% of cancer deaths[1]. HCC often results from cirrhosis or chronic liver injury caused by background diseases, such as hepatitis C virus (HCV), hepatitis B virus (HBV), primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), alcoholic liver disease, and nonalcoholic steatohepatitis (NASH). In the last 25 years, treatment for viral hepatitis has made great strides. Notably, HCV can be eliminated in almost all cases using direct-acting antivirals (DAAs). Although HBV is still an important risk factor that accounts for approximately 50% of the causes of HCC, the proportion of non-viral liver diseases, especially steatohepatitis, as the causative disease of HCC is increasing[2].

HCC is prone to recurrence, even if cured at an early stage. In the Barcelona Clinic Liver Cancer (BCLC) staging system[3-5], which is widely used in the treatment of HCC, early-stage HCC is classified as stage 0 or A. BCLC stage 0 is defined as very early stage, for single nodule ≤ 2 cm, Child-Pugh A, Eastern Cooperative Oncology Group Performance status (PS) 0. BCLC stage A is defined as the early stage and is the case of maximum tumor diameter ≤ 3 cm, number of tumors ≤ 3, Child-Pugh A-B, and PS 0. Liver transplantation is considered in some unresectable cases of stage A disease, but resection and ablation are often recommended as curative treatments. In recent years, a median overall survival > 6 years has been expected for early-stage liver cancer patients undergoing BCLC-0 of A liver resection and ablation[6]. However, even in the case of liver resection for early-stage HCC, the prognosis is poor in cases of portal hypertension[7,8].

Radiofrequency ablation (RFA) is the most widely used local therapy for HCC treatment. It has been reported that the 4-year local recurrence rate after RFA in the early stage is approximately 5%-10% and the 5-year survival rate is approximately 70%[9-13]. However, it has been reported that cases with impaired liver function and/or bad tumor conditions (large tumor diameter and large number of tumors) have a poor prognosis[13].

In recent years, many studies have demonstrated that sarcopenia is a poor prognostic factor in patients with chronic liver disease and HCC, because it is related to frailty, loss of function, and low quality of life. Sarcopenia is diagnosed using both muscle power loss and muscle volume loss according to the Japan Society of Hepatology (JSH) diagnostic guidelines or European diagnostic guidelines[14-16]. Pre-sarcopenia is defined as muscle volume loss without muscle power loss, and has been reported

to be a poor prognostic factor in the elderly population[17].

In addition, the usefulness of the Mac-2 binding protein glycosylation isomer (M2BPGi), or Wisteria floribunda agglutinin (WFA)-positive M2BP, which was first reported as a fibrosis marker in HCV patients, to treat HCC has recently attracted attention[18]. M2BPGi is a serum marker predicting fibrosis in HCV and other liver diseases, such as HBV, AIH, PBC, and NASH[19-22]. It is also a useful predictor of HCC in various liver diseases[23-27].

In this study, we investigated the usefulness of pre-sarcopenia, M2BPGi, and M2BP as recurrence and prognostic factors in patients who underwent RFA for early-stage HCC.

MATERIALS AND METHODS

Patients and data collection

A total of 202 patients underwent RFA for primary HCC between 2001 and 2017 at Hokkaido University Hospital, 160 of whom were diagnosed with BCLC stage 0 or A and followed up > 6 mo after RFA. Patients with HCV-RNA positive were classified to "HCV-positive" group and HCV-RNA negative were classified to "HCV-negative" group. Blood chemistry data, tumor factors (tumor number, size, and form), and clinical symptoms including ascites, pleural effusion, and hepatic encephalopathy were obtained before RFA.

Percutaneous RFA procedure

Percutaneous RFA was performed using a cooled-tip electrode (Cool-Tip; Ablation Systems, Covidien, Boulder, Colombia, CO) after ultrasonography (US) planning. RFA was performed by experienced operators under real-time ultrasound guidance. In some cases, we used a contrast-enhanced US technique or a real-time visual support system to detect the tumor more clearly. Moreover, in some cases, artificial ascites or pleural fluid can prevent thermal injury to extrahepatic organs or avoid the lungs in the tracking line. The ablation time, including three occurrences of roll-off, was 3-12 min. The ablated lesion and ablative margin were assessed using dynamic computed tomography (CT) or magnetic resonance imaging (MRI) 1-4 d after RFA.

Follow up and definition of recurrence of HCC

Because of the early detection of local and distant recurrence, the first imaging test (dynamic CT or MRI) after RFA was performed 4-8 wk after RFA. After the initial evaluation, follow-up by imaging (dynamic CT or MRI) and serum tumor markers such as alpha-fetoprotein (AFP), lens culinaris agglutinin-A reactive AFP isoform (AFP-L3), and des-γ-carboxy-prothrombin (DCP) were performed every 3-4 mo. Chest CT was regularly performed to detect distant metastases.

The treatment for recurrence and the definition of deaths

For HCC recurrence, appropriate treatment was performed according to liver cancer treatment guidelines[28-31]. Deaths due to liver cancer, liver failure (including acute or chronic liver failure), hemorrhage due to gastroesophageal varices, and infections associated with spontaneous bacterial peritonitis were defined as liver-related deaths. Deaths other than liver diseases, such as other organ cancers, ischemic heart disease, and pneumonia, were analyzed as survival sensors.

The diagnosis of pre-sarcopenia

Pre-sarcopenia was assessed according to the sarcopenia assessment criteria of the JSH guidelines for sarcopenia in liver disease[14]. Skeletal muscle mass index (SMI) calculated using simple methods[14, 16]. In particular, the left-right sum of the long axis times the short axis of the iliopsoas muscles at the level of the third lumbar vertebra (L3) divided by height squared. This method has been reported to correlate well with SMI calculated using a muscle mass measurement software.

Measurement of M2BPGi and M2BP

M2BPGi levels were measured in the conserved serum before RFA and at 1 mo after RFA. M2BPGi detection was based on a lectin-antibody sandwich immunoassay (Sysmex Co., Kobe, Japan) and expressed as a cutoff index (COI), with a range of 0.1-20 COI as previously reported[18].

M2BP was measured in conserved serum using enzyme-linked immunosorbent assay methods (Human Mac-2 binding protein (Mac-2bp) Assay Kit, Immuno-Biological Laboratories Co., Ltd., Fujioka, Japan).

Statistical analysis

Statistical analyses were performed using EZR software[32]. The Mann-Whitney U test was used to analyze continuous variables. Fisher's exact test was used for univariate analysis of ordered variables. The Kaplan-Meier method was used to determine recurrence and survival rates, and the log-rank test was used to analyze differences. The median value was used as the cutoff. For the multivariate analysis

of factors related to recurrence and survival, Cox proportional hazards models with stepwise methods using *P* value were used.

Ethical considerations

The study protocol was approved by the Institutional Ethics Committee of Hokkaido University (IRB-No. 015-1412) and conformed to the ethical guidelines of the Declaration of Helsinki.

RESULTS

Patient characteristics

As shown in Figure 1, 202 patients underwent RFA for primary HCCs. Of these, 160 cases were classified as BCLC stage 0 or A, and the data were analyzed. Eighty-three patients were classified into the HCV-positive group, and 77 patients were classified into the HCV-negative group. The ratio of older age and Child-Pugh Grade B was higher in the HCV-positive group than in the HCV-negative group. Serum transaminase and fibrosis-4 (FIB-4) index were higher in the HCV-positive group than in the HCV-negative group. In addition, the serum AFP and AFP-L3 levels were higher in the HCV-positive group. The median tumor diameter and number were not significantly different; however, they tended to be larger in the HCV-positive group than in the HCV-negative group. In contrast, the SMI of the HCV-positive group was significantly lower than that of the HCV-negative group (Table 1).

M2BP and M2BPGi values in HCV-positive and -negative patients

In the HCV-positive group, the median M2BP was 5385 ng/mL and that of M2BPGi was 4.94 COI. On the other hand, in the HCV-negative group, the median M2BP was 2745 ng/mL and that of M2BPGi was 1.86 COI. M2BP and M2BPGi levels were significantly higher in the HCV-positive group than in the negative group (Figure 2). Therefore, we used the median as the cutoff value in the following analysis for each group.

M2BPGi, not M2BP, is the risk factor of recurrence in HCV-negative patients

Next, we examined whether M2BP and M2BPGi could be predictive factors for HCC recurrence in primary HCC patients with BCLC stage 0 or A. M2BP could not be a predictive factor for HCC recurrence in each group, but M2BPGi could be a clinical predictor for HCC recurrence only in the HCV-negative group (Figure 3). Therefore, it is suggested that M2BPGi, but not M2BP, is a predictive factor for HCC recurrence in patients without current HCV infection.

Higher M2BPGi levels and pre-sarcopenia are risk factors for liver-related death in HCV-negative patients

For further analysis, we examined whether M2BP and M2BPGi could be predictive factors of liver-related death in BCLC stage 0 or A. In the HCV-positive group, older age ($\geq$ 70 years), albumin-bilirubin (ALBI) grade 2 or 3, DCP $\geq$ 23 mAU/L, and AFP-L3 $\geq$ 10% were factors contributing to a negative effect on survival on univariate analysis. Only DCP $\geq$ 23 mAU/L was a factor contributing to a negative effect on survival on multivariate analysis, and higher M2BP and M2BPGi were not significant factors for a negative effect on survival in the HCV-positive group (Table 2). In contrast, in the HCV-negative group, M2BPGi $\geq$ 1.86 COI and pre-sarcopenia were significant factors contributing to a negative effect on survival (Table 3). In the HCV-negative patient group, M2BPGi, but not M2BP, was a poor prognostic factor (Figure 4). Similarly, pre-sarcopenia was a poor prognostic factor only in the HCV-negative group (Figure 5). Therefore, higher M2BPGi and pre-sarcopenia were poor prognostic factors in patients without active HCV infection.

DISCUSSION

In this study, we retrospectively analyzed the prognostic factors of early-stage HCC (BCLC stage 0-A) after RFA treatment. Here, we investigated the usefulness of M2BGi and M2BP as predictors of HCC recurrence and prognosis. As a result, M2BPGi and pre-sarcopenia were useful in HCC recurrence and as prognostic factors in patients without current HCV infection.

Many randomized controlled trials[11,33-40] have compared the treatment outcomes of hepatectomy and RFA for early-stage HCC, but there are few reports with high quality evidence[11,39,40]. In recent years, Ng *et al*[11] reported no statistically significant difference in recurrence-free survival between hepatectomy and RFA in 109 cases. In the SURF trial, hepatectomy and RFA for HCC with a Child-Pugh score $\leq$ 7, tumor diameter $\leq$ 3 cm, and tumor number $\leq$ 3 had equivalent recurrence-free survival[39]. Based on the above, RFA has almost the same therapeutic results as hepatectomy for BCLC stage 0/A HCC. Considering that RFA is less invasive than hepatectomy, it is expected to become a standard

Table 1 Patient characteristics

	HCV-positive (*n* = 83)	HCV-negative (*n* = 77)	*P* value
Sex (male/female)	45/38	50/27	0.20
Age (years)[1]	70 (44-90)	64 (41-88)	< 0.01
Tumor factors			
Tumor number (solitary/multiple)	63/20	68/9	0.07
Tumor size (mm)[1]	17 (8-30)	15 (6-30)	0.05
Tumor form (only boundary/others)	67/16	68/9	0.20
Stage (LCSG) (I/II/III)	39/38/6	45/27/5	0.35
Liver function			
Child-Pugh Score (5-6/7-9)	66/17	66/11	< 0.01
ALBI grade (1/2-3)	27/56	43/34	0.41
Blood data			
Platelet (×10^4/μL)[1]	10.2 (2.7-43.7)	11.8 (3.7-36.8)	0.04
AST (U/L)[1]	56 (18-139)	39 (16-100)	< 0.01
ALT (U/L)[1]	49 (12-155)	30 (9-87)	< 0.01
FIB-4 index[1]	5.90 (0.96-37.86)	3.61 (0.88-14.16)	< 0.01
APRI[1]	2.00 (0.15-15.06)	1.08 (0.28-4.32)	< 0.01
PT (%)[1]	84.6 (48.6-125.0)	81.3 (51.8-117.1)	0.51
Total bilirubin (mg/dL)[1]	0.9 (0.2-2.8)	0.9 (0.4-2.7)	0.56
Albumin (g/dL)[1]	3.7 (2.2-4.7)	4.0 (2.4-5.0)	< 0.01
AFP (ng/mL)[1]	17.4 (3.0-621.6)	6.4 (1.3-1962.9)	< 0.01
DCP (mAU/mL)[1]	23 (4-1086)	22 (7-6308)	0.66
AFP-L3 (%)[1]	5.1 (< 0.5-69.1)	< 0.5 (< 0.5-85.6)	0.03
M2BPGi (COI)[1]	4.94 (0.78-17.81)	1.86 (0.36-10.23)	< 0.01
M2BP (ng/mL)[1]	5385 (1460-22770)	2745 (865-12150)	< 0.01
SMI (cm^2/m^2)[1]	5.28 (2.62-11.75)	6.51 (2.58-10.89)	< 0.01
Pre-sarcopenia, *n* (%)	21 (25.3)	14 (18.2)	0.34
Observation period (mo)[1]	46 (6-157)	56 (6-185)	0.19

[1]Median (range).

APRI (AST to platelet ratio index) = AST/platelet. FIB4 index = (age × AST)/(platelet × alanine aminotransferase × 0.5). HCV: hepatitis C virus; LCSG: liver cancer study group; ALBI: albumin-bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PT: prothrombin time; AFP: alfa-fetoprotein; DCP: des-γ-carboxyprothrombin; M2BPGi: Mac-2 binding protein glycosylation isomer; M2BP: Mac-2 binding protein; SMI: skeletal muscle mass index.

treatment.

However, it has been reported that local recurrence is observed in approximately 10% of cases in which a sufficient ablation area is obtained by RFA[41,42]. The risk factors for recurrence have also been reported. Shiina *et al*[13] reported that, in a large number of cases, a higher DCP was associated with local recurrence. Ectopic recurrence is associated with HCV positivity, Child-Pugh grade B or C, platelet counts ≤ 100000, higher AFP, higher DCP, large tumor diameter, and a large number of tumors. Thus, regarding the recurrence of HCC after RFA, not only tumor factors but also factors related to liver function are largely involved. Contrarily, factors related to survival after RFA including younger age, lack of portosystemic shunt, Child-Pugh grade A, lower bilirubin, lower ALBI score, higher albumin, higher prothrombin time, lower AFP, HBV positivity, lower neutrophil to lymphocyte ratio, small tumor diameter, and low tumor number have been reported in a meta-analysis[43]. Therefore, liver function and pretreatment tumor factors are considered important factors not only for recurrence but also for survival.

Table 2 Factors contributing to survival in hepatitis C virus-positive patients

Subject	Univariate	Multivariate		
	P value	HR	95%CI	*P* value
Age (< 70/≥ 70 years)	0.08	1.92	0.94-3.94	0.074
Sex (Female/Male)	0.13			
ALBI grade (1/2,3)	0.06	1.81	0.84-3.90	0.129
Child-Pugh Score (5-6/7-15)	0.15			
Stage (LCSG) (I/II+III)	0.47			
Tumor number (solitary/multiple)	0.97			
Tumor form (only boundary/others)	0.43			
Tumor size (< 20 mm/≥ 20 mm)	0.54			
AFP (< 17.2/≥ 17.2 ng/mL)	0.12			
DCP (< 23/≥ 23 mAU/mL)	< 0.01	2.54	1.23-5.23	0.012
AFP-L3 (< 10/≥ 10%)	0.02	1.72	0.80-3.71	0.167
M2BPGi (< 4.94/≥ 4.94 COI)	0.26			
M2BP (< 5385/≥ 5385 ng/mL)	0.24			
APRI (< 2.0/≥ 2.0)	0.58			
FIB-4 index (< 4.5/≥ 4.5)	0.31			
Pre-sarcopenia (No/Yes)	0.28			

APRI (AST to platelet ratio index) = AST/platelet. FIB4 index = (age × AST)/(platelet × alanine aminotransferase × 0.5). HR: hazard ratio; CI: confidence interval; ALBI: albumin-bilirubin; LCSG: liver cancer study group; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PT: prothrombin time; AFP: alfa-fetoprotein; DCP: des-γ-carboxyprothrombin; M2BPGi: Mac-2 binding protein glycosylation isomer; COI: cutoff index; M2BP: Mac-2 binding protein.
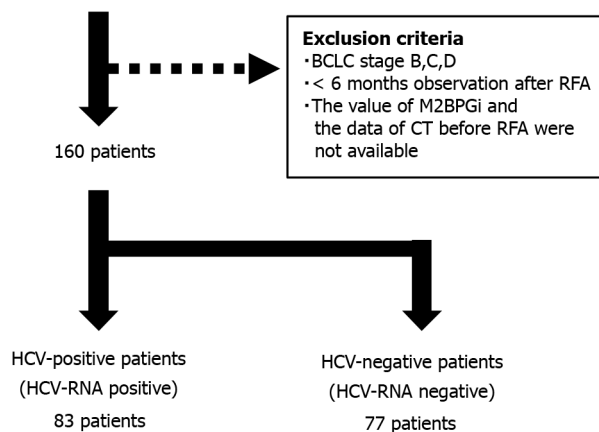
Figure 1 Patients' flow. HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; RFA: Radiofrequency ablation; BCLC: Barcelona Clinic Liver Cancer; CT: Computed tomography.

In this study, we focused on M2BPGi and muscle mass, which are not direct tumor factors and liver function. M2BP is a secreted glycoprotein of approximately 90 kDa that was originally reported as a ligand for galectin[44]. The serum concentration of M2BP has been reported to increase in various cancers, such as breast and lung cancers[45]. Furthermore, Kamada *et al*[46] reported its usefulness as a marker of liver fibrosis in patients with non-alcoholic fatty liver disease. M2BPGi has a sugar chain with an affinity for WFA and distinguishes the glycan structure of WFA-detectable M2BP. The usefulness of M2BPGi as a marker of liver fibrosis in patients with HCV infection was reported in 2013[18]. M2BPGi has also been reported to be useful as a fibrosis marker in various liver diseases[19-22]. However, the

Table 3 Factors contributing to survival in hepatitis C virus-negative patients

Subject	Univariate	Multivariate		
	P value	HR	95%CI	*P* value
Age (< 65/≥ 65)	0.03	-		
Sex (Female/Male)	0.88			
ALBI grade (1/2,3)	< 0.01	2.41	0.81-7.12	0.115
Child-Pugh Score (5-6/7-15)	< 0.01	-		
Stage (LCSG) (I/II+III)	0.91			
Tumor number (solitary/multiple)	0.54			
Tumor form (boundary/others)	0.11			
Tumor size (< 20 mm/≥ 20 mm)	0.74			
AFP (< 6.4/≥ 6.4 ng/mL)	0.64			
DCP (< 22/≥ 22 mAU/mL)	0.23			
AFP-L3 (< 10/≥ 10%)	0.29			
M2BPGi (< 1.86/≥ 1.86 COI)	< 0.01	4.89	1.97-12.18	< 0.001
M2BP (< 2745/≥ 2745 ng/mL)	0.92			
APRI (< 1.5/≥ 1.5)	0.04	-		
FIB-4 index (< 3.6/≥ 3.6)	< 0.01	1.86	0.63-5.44	0.257
Pre-sarcopenia (no/yes)	0.04	3.34	1.19-9.37	0.022

APRI (AST to platelet ratio index) = AST/platelet. FIB4 index = (age × AST)/(platelet × alanine aminotransferase × 0.5). HR: hazard ratio; CI: confidence interval; ALBI: albumin-bilirubin; LCSG: liver cancer study group; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PT: prothrombin time; AFP: alfa-fetoprotein; DCP: des-γ-carboxyprothrombin; M2BPGi: Mac-2 binding protein glycosylation isomer; COI: cutoff index; M2BP: Mac-2 binding protein.
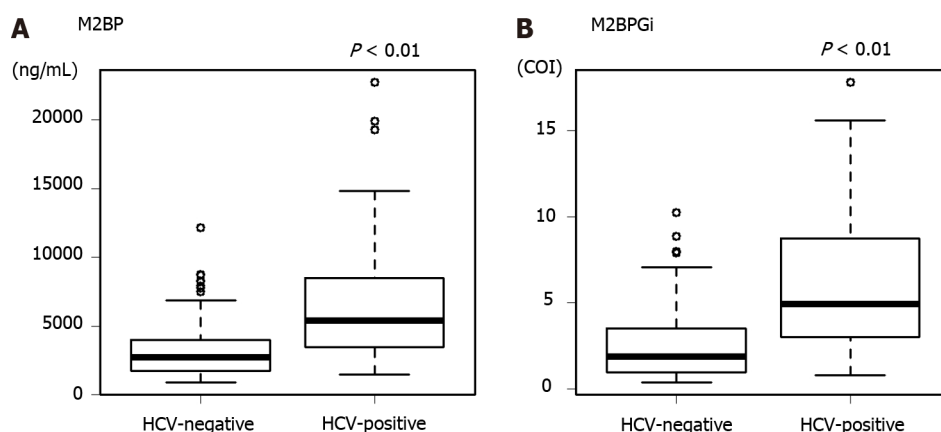
Figure 2 The value of Mac-2 binding protein and Mac-2 binding protein glycosylation isomer in hepatitis C virus-positive and -negative patients. A: The values of Mac-2 binding protein in hepatitis C virus (HCV)-negative and -positive groups; B: The values of Mac-2 binding protein glycosylation isomer in HCV-negative and -positive groups. The box charts for the Y-axis indicate the median as TextTitle lines in the boxes, 25th and 75th percentiles as boxes, and 10th and 90th percentiles as lines for each edge. HCV: Hepatitis C virus; M2BPGi: Mac-2 binding protein; M2BPGi: Mac-2 binding protein glycosylation isomer; COI: Cutoff index.

M2BPGi value differs depending on the background liver disease, and it has been reported that the predicted cutoff value of METAVIR scoring system in the F4 stage is 5.2 COI for HCV, 3.1 COI for HBV, and 0.91 COI for NASH[47,48]. M2BPGi is an interferon (IFN)-simulated protein, and the amount of M2BPGi decreases after HCV eradication[49]. Therefore, it is suggested that M2BPGi is high in patients currently infected with HCV, even with the same degree of liver fibrosis. In this study, the median values differed significantly between the HCV-positive and HCV-negative patients. The M2BPGi levels were significantly higher in HCV-positive patients than in HCV-negative patients (Figure 2). Therefore,
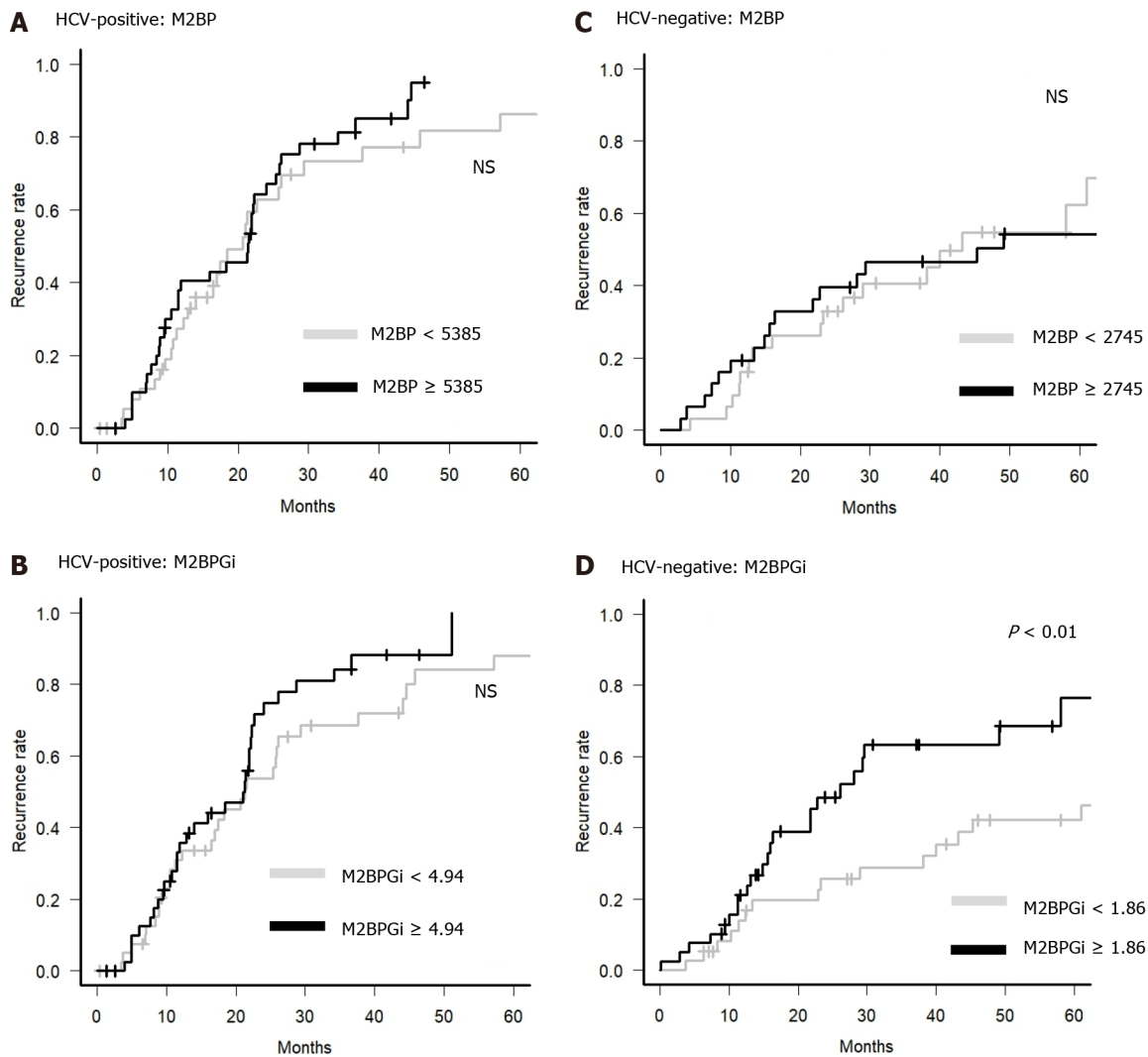
Figure 3 Recurrence rate according to the value of Mac-2 binding protein and Mac-2 binding protein glycosylation isomer. The hepatocellular carcinoma recurrence rate was divided into two groups according to the value of Mac-2 binding protein (M2BP) or M2BP glycosylation isomer (M2BPGi) before radiofrequency ablation. A: Hepatitis C virus (HCV)-positive group divided by M2BP value. The gray line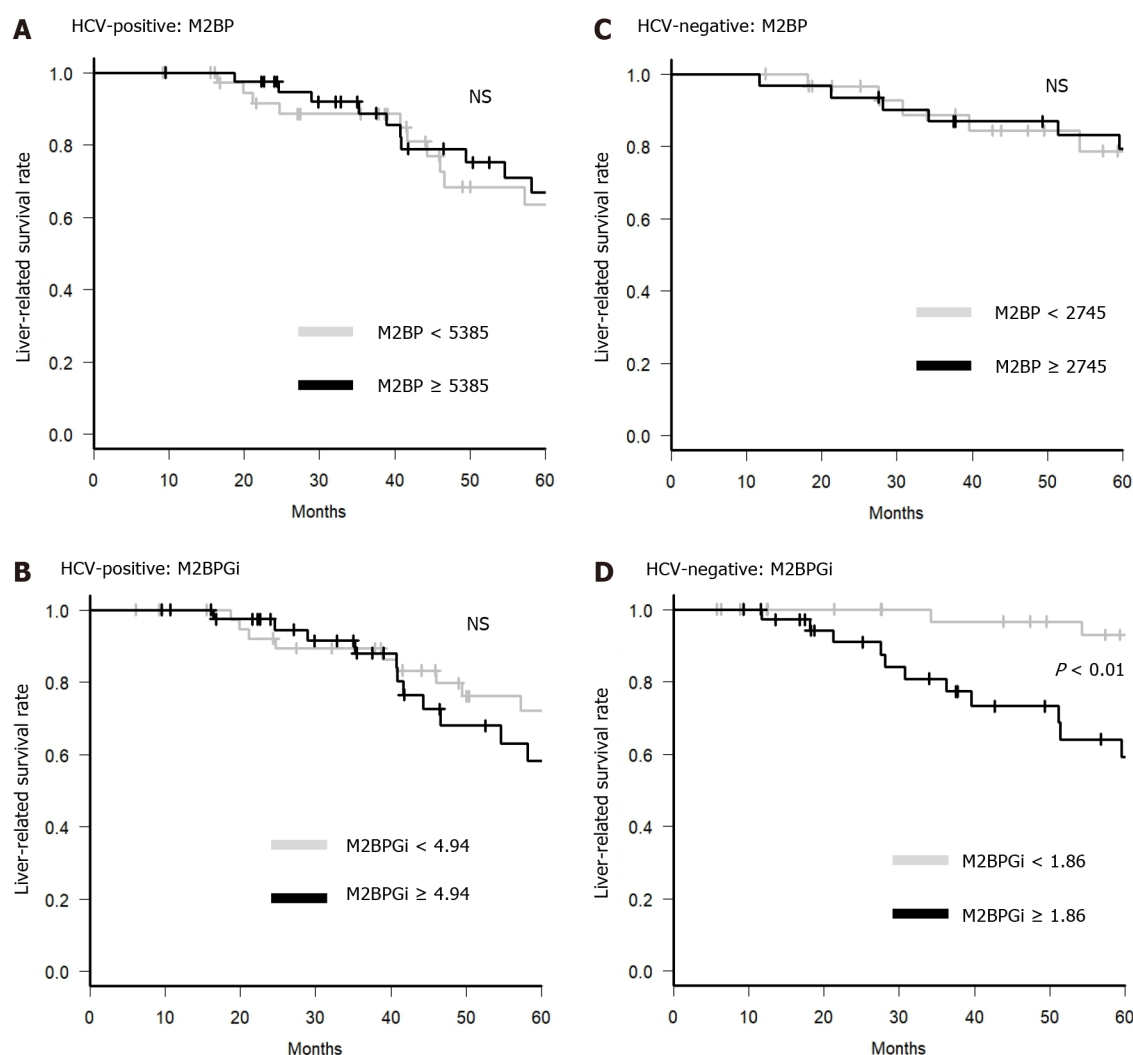 indicates patients with M2BP < 5385 ng/mL, and the black line indicates patients with M2BP ≥ 5385 ng/mL; B: HCV-positive group divided by M2BPGi value. The gray line indicates patients with M2BPGi < 4.94 cutoff index (COI), and the black line indicates patients with M2BPGi ≥ 4.94 COI; C: HCV-negative group divided by M2BP value. The gray line indicates patients with M2BP < 2745 ng/mL, and the black line indicates patients with M2BP ≥ 2745 ng/mL; D: HCV-negative group divided by M2BPGi value. The gray line indicates patients with M2BP < 1.86 COI, and the black line indicates patients with M2BPGi ≥ 1.86 COI. HCV: Hepatitis C virus; M2BPGi: Mac-2 binding protein; M2BPGi: Mac-2 binding protein glycosylation isomer; NS: No significance.

we analyzed the M2BPGi values separately in HCV-positive and HCV-negative patients.

M2BPGi has also been reported as a useful marker for predicting the occurrence of HCC. Specifically, it has been reported as a marker for predicting HCC in HCV, HBV and post-HCV eradication cases[19, 23,25,27,49-57]. In this study, M2BPGi significantly predicted recurrence in HCV-negative cases. In contrast, M2BP level was not be a predictor of recurrence. Progression of liver fibrosis is a risk factor for HCC. As M2BPGi reflects liver fibrosis, M2BPGi may be indirectly associated with the development of HCC. M2BPGi may show higher levels in HCV cases than in others, even at similar levels of liver fibrosis. This is because the inflammation caused by the current HCV infection might affect the M2BPGi value in the HCV-positive group. Therefore, predicting HCC recurrence may be difficult using the value of M2BPGi only in HCV-positive cases. Based on the results of this study, prediction of cases at a high risk for recurrence after RFA was possible in early-stage HCC by focusing on the value of M2BPGi in HCV-negative patients.

Furthermore, M2BPGi has been reported to be a useful marker for predicting the prognosis of patients after HCV eradication, hepatectomy, and transcatheter arterial chemoembolization[25,58,59]. In this study, we analyzed prognostic factors after RFA for early-stage HCC, focusing on M2BP, M2BPGi, and pre-sarcopenia. In HCV-positive cases, DCP that is one of the serum tumor markers of HCC was a significant poor prognosis factor. In contrast, in HCV-negative cases, M2BPGi and pre-sarcopenia were significant poor prognostic factors, but tumor factors (tumor number, size, form, and serum markers) were not. In addition, M2BP was not a prognostic predictor in either group. M2BPGi levels are affected
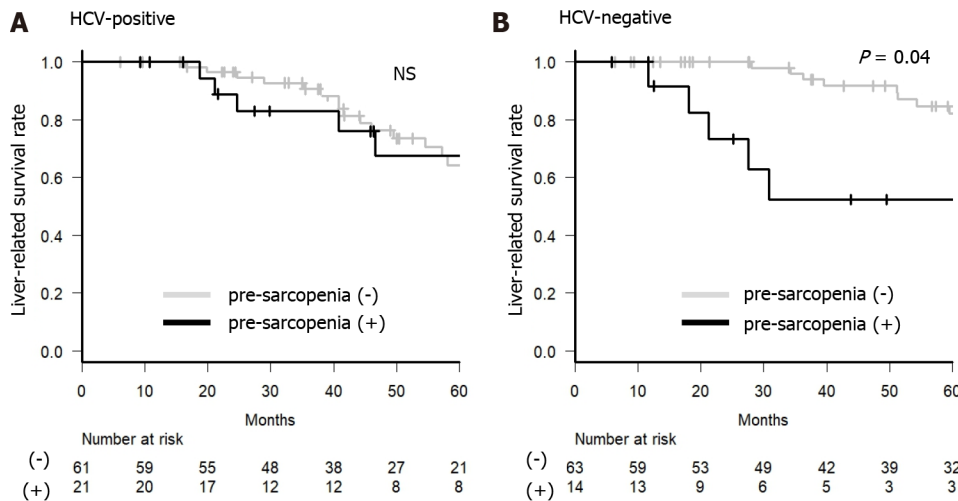
Figure 4 Survival rate according to the value of Mac-2 binding protein and Mac-2 binding protein glycosylation isomer. The liver disease-related death-free survival rate was divided into two groups according to the value of Mac-2 binding protein (M2BP) or M2BP glycosylation isomer (M2BPGi) before radiofrequency ablation. A: Hepatitis C virus (HCV)-positive patients divided by M2BP value. The gray line indicates patients with M2BP < 5385 ng/mL, and the black line indicates patients with M2BP ≥ 5385 ng/mL; B: HCV-positive patients divided by M2BPGi value. The gray line indicates patients with M2BPGi < 4.94 cutoff index (COI), and the black line indicates patients with M2BPGi ≥ 4.94 COI; C: HCV-negative patients divided by M2BP value. The gray line indicates patients with M2BP < 2745 ng/mL, and the black line indicates patients with M2BP ≥ 2745 ng/mL; D: HCV-negative patients divided by M2BPGi value. The gray line indicates patients with M2BPGi < 1.86 COI, and the black line indicates patients with M2BPGi ≥ 1.86 COI. HCV: Hepatitis C virus; M2BPGi: Mac-2 binding protein; M2BPGi: Mac-2 binding protein glycosylation isomer; NS: No significance.

by various factors, including acute liver failure, and are associated with liver inflammation, damage, and hepatocyte degeneration[60]. Furthermore, M2BPGi was reported to correlate with inflammatory cytokines and was reduced by steroid treatment in patients with autoimmune hepatitis[61]. In HCV-negative cases, high M2BPGi levels may indicate advanced fibrosis or coexistence of inflammation because these cases are not affected by HCV. Therefore, M2BPGi may be a predictor of liver-related death. Notably, M2BPGi was a more sensitive prognostic marker than other liver function or fibrosis markers such as ALBI and FIB-4 in HCV-negative patients. Thus, M2BPGi may be a marker that can predict poor prognosis, including the effects of other factors, such as inflammation and liver fibrosis.

Patients with chronic liver disease and sarcopenia have a significantly poorer prognosis[62]. Furthermore, it has been reported that in the elderly, pre-sarcopenia cases have a poorer prognosis than non-sarcopenia cases[17]. In this study, pre-sarcopenia was a significant poor prognostic factor in HCV-negative cases but was not a significant prognostic factor in HCV-positive cases. The reason for this might be related to the fact that HCV-positive patients had significantly less SMI than the HCV RNA-negative patient group (Table 1). Because muscle volume increases after IFN-free treatment in HCV-positive patients and HCV elimination suppresses pre-sarcopenia, the current HCV infection itself may contribute to pre-sarcopenia. In this study, the high proportion of cases of pre-sarcopenia and the elderly may have affected the observation that pre-sarcopenia was not a significant prognostic factor in HCV-positive cases[63,64].

Figure 5 Survival rate with or without pre-sarcopenia. The liver disease-related survival rate was divided into two groups according to the presence of pre-sarcopenia before radiofrequency ablation. A: Hepatitis C virus (HCV)-positive group; B: HCV-negative group. The gray line indicates patients without pre-sarcopenia, and the black line indicates patients with pre-sarcopenia. The numbers under each group indicate the number at risk for each group. HCV: Hepatitis C virus; M2BPGi: Mac-2 binding protein; M2BPGi: Mac-2 binding protein glycosylation isomer; NS: No significance.

This study has several limitations. First, it was a retrospective observational study involving a single hospital and a small number of patients. Second, SMI was evaluated using only the simple CT method. Further studies with larger patient numbers and multicenter evaluations are needed.

CONCLUSION

In the near future, almost all HCVs will be eradicated by DAA treatment. Henceforth, almost no HCC cases were derived from the current HCV infection. In this study, we investigated the predictive factors of survival after RFA for HCC in BCLC stage 0 or A patients divided into two groups: HCV-RNA positive and negative. Pre-sarcopenia and M2BPGi, but not M2BP, might be useful tools for the prediction of survival in early-stage HCC in the era of HCV eradication.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is prone to recurrence, even if cured at an early stage. In recent years, many studies have demonstrated that sarcopenia is a poor prognostic factor in patients with chronic liver disease and HCC, because it is related to frailty, loss of function, and low quality of life. Pre-sarcopenia is defined as muscle volume loss without muscle power loss and is a poor prognostic factor in the elderly population. In addition, the usefulness of the Mac-2 binding protein glycosylation isomer (M2BPGi), or Wisteria floribunda agglutinin-positive M2BP, which was first reported as a fibrosis marker in hepatitis C virus (HCV) patients, to treat HCC has recently attracted attention.

Research motivation

The M2BPGi, a fibrosis marker in various liver diseases, is reportedly a prognostic marker in patients with HCC who underwent hepatectomy. In recent years, many studies have demonstrated that sarcopenia is a poor prognostic factor in patients with chronic liver disease and HCC, because it is related to frailty, loss of function, and low quality of life. Sarcopenia is diagnosed using both muscle power loss and muscle volume loss. Pre-sarcopenia is defined as muscle volume loss without muscle power loss and is a poor prognostic factor in the elderly population.

Research objectives

To investigate the usefulness of pre-sarcopenia, M2BPGi, and M2BP as recurrence and prognostic factors in patients who underwent RFA for early-stage HCC.

Research methods

In this study, 202 patients underwent radiofrequency ablation (RFA) for primary HCCs. Of these, 160

cases were classified as BCLC stage 0 or A, and the data were analyzed. Eighty-three patients were classified into the HCV-positive group, and 77 patients were classified into the HCV-negative group.

Research results
In HCV-positive patients, only des-γ-carboxy-prothrombin (DCP) ≥ 23 mAU/mL was a significant poor prognostic factor affecting survival after RFA. In HCV-negative patients, M2BPGi ≥ 1.86 cutoff index was significantly associated with tumor recurrence, but M2BP was not. M2BPGi ≥ 1.86 cutoff index (hazard ratio, 4.89; 95% confidence interval: 1.97-12.18; $P < 0.001$) and pre-sarcopenia (hazard ratio, 3.34, 95% confidence interval: 1.19-9.37; $P = 0.022$) were independent significant poor prognostic factors in HCV-negative patients.

Research conclusions
In HCV-negative patients with primary HCC treated with RFA, lower M2BPGi contributed to a lower tumor recurrence rate and longer survival period. Pre-sarcopenia contributed to the poor prognosis independently in HCV-negative patients.

Research perspectives
In the near future, almost all HCVs will be eradicated by DAA treatment. Almost no HCC cases were derived from the current HCV infection. Pre-sarcopenia and M2BPGi, but not M2BP, might be useful tools to predict survival in early-stage HCC in the era of HCV eradication.

FOOTNOTES

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