



ORIGINAL ARTICLE

Elevation of Mac-2 binding protein glycosylation isomer after hepatectomy is associated with post-hepatectomy liver failure, total Pringle time, and renal dysfunction

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Abstract

Background: Mac-2 binding protein glycosylation isomer (M2BPGi) is a novel serum glycomarker used to assess liver fibrosis. However, it has been reported that M2BPGi is likely to reflect other factors not limited to liver fibrosis.

Methods: We retrospectively analyzed 79 patients with liver tumors who underwent liver resection. M2BPGi was measured within 1 week before operation and almost 1 month after operation. We introduced a value termed the “ Δ M2BPGi ratio” ($=\text{M2BPGi}_{\text{after operation}}/\text{M2BPGi}_{\text{before operation}}$), and analyzed factors that influenced the Δ M2BPGi ratio.

Results: The median value of the Δ M2BPGi ratio was 1.28 (range, 0.36-5.68). In 64 patients (81.0%), the cutoff index values of M2BPGi were elevated approximately 1 month after operation, especially in patients who experienced post-hepatectomy liver failure (PHLF). Multiple linear regression showed total Pringle time, PHLF grade \geq B, and preoperative value of creatinine were significant predictors of the Δ M2BPGi ratio. The mean values of the Δ M2BPGi ratio were 1.37 ± 0.07 , 1.52 ± 0.22 , and 2.94 ± 0.30 for PHLF grade 0, grade A, and grade B, respectively, resulting in statistically significant differences by the Kruskal-Wallis test ($P = 0.022$).

Conclusions: Total Pringle time, PHLF grade \geq B, and preoperative creatinine significantly influenced the elevation of M2BPGi almost 1 month after liver resection. This study strongly affirms the previous suggestion that M2BPGi is likely to reflect other factors not limited to liver fibrosis.

KEYWORDS

liver resection, Mac-2 binding protein glycosylation isomer, post-hepatectomy liver failure, Pringle maneuver, renal dysfunction

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1 | INTRODUCTION

Mac-2 binding protein glycosylation isomer (M2BPGi) is a novel serum glycomarker used to assess liver fibrosis in patients infected with chronic hepatitis C¹⁻³ or B virus^{4,5} as well as in patients with primary biliary cirrhosis,^{6,7} biliary atresia,⁸ autoimmune hepatitis,⁹ and non-alcoholic fatty liver disease.¹⁰⁻¹²

Although M2BPGi level correlates with liver fibrosis, M2BPGi levels immediately decrease following the eradication of hepatitis C virus (HCV) by direct-acting antiviral therapy, whereas the rapid improvement of liver fibrosis beyond 24 weeks post-treatment is unlikely.¹³ Furthermore, M2BPGi was increased in patients with acute liver injury and decreased after their recovery.¹⁴ These observations suggest that M2BPGi reflects liver fibrosis and other factors such as liver inflammation, liver damage, and hepatocyte regeneration.

In this study, we measured serum M2BPGi levels in patients who underwent liver resection for liver tumors before and approximately 1 month after operation. Our aims were to analyze which factors influence perioperative changes in the M2BPGi value, and to evaluate the biological features of M2BPGi.

2 | MATERIALS AND METHODS

2.1 | Patients

Between December 2016 and December 2018, 120 consecutive patients underwent liver resection for liver tumor at Hiroshima Red Cross Hospital & Atomic Bomb Survivors Hospital. Of these, patients who underwent open microwave ablation without liver resection (four) and patients with a lack of pre- or postoperative M2BPGi test results (33) were excluded from this study. Four patients who underwent postoperative M2BPGi testing over 1 month after operation were also excluded for data accuracy. Consequently, 79 patients were eligible for this study.

A preoperative serum sample was collected at the time of admission for liver resection within 1 week before surgery, and a postoperative sample was collected at the outpatient clinic approximately 1 month after liver resection. M2BPGi values were measured at SRL (Tokyo, Japan), and reported as the cutoff index (COI). We introduced a value termed the "ΔM2BPGi ratio" ($=\text{M2BPGi}_{\text{after operation}} / \text{M2BPGi}_{\text{before operation}}$) for perioperative changes in the M2BPGi value. We also analyzed predictors of the ΔM2BPGi ratio. Other serologic fibrosis markers, 7S domain of type IV collagen (4COL7S) and hyaluronic acid were also measured at SRL.

Post-hepatectomy liver failure (PHLF) was diagnosed on the basis of the International Study Group of Liver Surgery definition.¹⁵ Briefly, elevated prothrombin time - international normalization ratio and concomitant hyperbilirubinemia on or after postoperative day 5 was defined as PHLF. The severity of PHLF was graded as follows: Grade A, PHLF that required no change in a patient's clinical management; Grade B, PHLF that required

a deviation from the regular course but did not require invasive therapy; and Grade C, PHLF that required invasive treatment including intensive care.

The study protocol was approved by our institutional ethics committee.

2.2 | Statistical analysis

All statistical analyses were performed using SAS software (JMP 13.0.1; SAS Institute Inc., Cary, NC, USA). Continuous variables were expressed as the means ± standard deviations or medians with ranges, and compared using Student's t-test. Categorical variables were compared using the Chi-square test or Fisher exact test as required. The difference among PHLF grades and between paired stages was compared using the Kruskal-Wallis test and the Wilcoxon rank-sum test, respectively. In multiple linear regression, predictors were selected through a stepwise procedure using the minimum Bayesian information criterion (BIC) method among the factors selected in single linear regression.

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics, tumor status, and summary of the postoperative course are summarized in Table 1. The study population consisted of 55 men and 24 women with a median age of 72 years (range, 36-91). Among these patients, 30 (38.0%) were positive for HCV antibody, 22 (27.8%) were positive for HBV surface antigen, and 27 (34.2%) were negative for both (nonBnonC). The Child-Pugh score was 5 in 59 (74.7%) patients, 6 in 16 (20.3%) patients, and 7 in four (5.1%) patients.

The median operative time was 224 minutes (range, 111-488), with a median total Pringle time of 49 minutes (range, 0-150) and median blood loss of 234 g (range 0-2247). Blood transfusion was performed in four (5.0%) patients. The type of hepatectomy included nonanatomical partial resection and subsegmentectomy in 34 (43.0%) patients each, sectionectomy in eight (10.1%), and lobectomy in three (3.8%).

The pathological diagnosis of the liver tumor was hepatocellular carcinoma (HCC) in 59 patients (74.7%), combined hepatocellular cholangiocellular carcinoma and intrahepatic cholangiocarcinoma in six each, and metastatic tumor and benign tumor in four each. The median diameter of the largest tumor was 2.2 cm (range, 0.7-13), and the median tumor number was one (range, 1-3). Pathological F4 was observed in 37 patients (48.1%).

The median length of postoperative hospital stay was 12 days (range, 7-30). Twenty-eight (46.4%) patients experienced postoperative complications: Clavien-Dindo Class I in 15 (19.5%) patients, Class II in 12 (15.6%), and Class IV in one (1.3%). PHLF occurred in 11 patients (13.9%): Grade A in seven (8.9%) and Grade B in four (3.0%).

TABLE 1 Patient demographic and clinical characteristics

Factors	Total cases (n = 79)
Sex, male (%)	55 (69.6)
Age, years	72 (36-91)
Etiology (%)	
HCV	30 (38.0)
HBV	22 (27.8)
nonBnonC	27 (34.2)
Child-Pugh score (%)	
5	59 (74.7)
6	16 (20.3)
7	4 (5.1)
Operative factors	
Operative time (min)	224 (111-488)
Total Pringle time (min)	49 (0-150)
Blood loss (mL)	234 (0-2227)
Blood transfusion (%)	4 (5.0)
Liver resection (%)	
Partial hepatectomy	34 (43.0)
Subsegmentectomy	34 (43.0)
Sectionectomy	8 (10.1)
Lobectomy	3 (3.8)
Pathological findings (%)	
HCC	59 (74.7)
Combined HCC-CCA	6 (7.6)
ICC	6 (7.6)
Metastatic tumor	4 (5.0)
Benign tumor	4 (5.0)
Tumor size (cm)	2.2 (0.7-13)
Single tumor (%)	58 (75.3)
F factor (%)	
0	6 (7.8)
1	4 (6.5)
2	13 (16.9)
3	17 (20.8)
4	37 (48.1)
Postoperative course	
Postoperative hospital stay, days	12 (7-30)
Clavien-Dindo classification (%)	
0	49 (63.6)
I	15 (19.5)
II	12 (15.6)
III	0
IV	1 (1.3)
V	0

(Continues)

TABLE 1 (Continued)

Factors	Total cases (n = 79)
Post-hepatectomy liver failure (%)	
0	68 (86.1)
A	7 (8.9)
B	4 (5.0)
C	0

Abbreviations: CCA, cholangiocarcinoma; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICC, intrahepatic cholangiocarcinoma.

3.2 | Performance of M2BPGi as a marker for liver fibrosis

The mean COI value of preoperative M2BPGi was 1.78 ± 1.41 . The M2BPGi level was positively correlated with pathological fibrosis stage (Figure 1). The mean COI values were 0.80 ± 0.51 , 0.98 ± 0.62 , 0.94 ± 0.35 , 1.39 ± 0.30 , and 2.55 ± 0.20 in stages F0, F1, F2, F3, and F4 patients, respectively, resulting in a statistically significant difference by Kruskal-Wallis test ($P < 0.001$). Differences between the abutting stages were significant between F3 and F4 ($P = 0.001$, Wilcoxon rank-sum test).

3.3 | The relationship between pre- and postoperative M2BPGi

The mean postoperative M2BPGi value was 2.32 ± 1.63 . The median number of days between operation and serum sampling was 22 days (range, 18-29). The relationship between pre- and postoperative M2BPGi is shown in Figure 1. The postoperative M2BPGi values were strongly correlated to preoperative values ($R^2 = 0.77$, $P < 0.001$). The median value of the $\Delta M2BPGi$ ratio was 1.28 (range 0.36-5.68). In 64 patients (81.0%), the M2BPGi values were elevated after operation, especially in patients who experienced PHLF (Figure 2).

In addition, it should be noted that we had one patient whose M2BPGi value markedly dropped after liver resection (Figure 2). Her preoperative COI value of M2BPGi was 2.23 and dropped to 0.8 after operation ($\Delta M2BPGi$ ratio = 0.36). The patient was 72 years old and underwent S8 partial hepatectomy for colorectal liver metastases. Her preoperative liver function was normal with Child-Pugh score of 5; indocyanine green retention rate at 15 minutes, 21.2; platelet count, $11.2 \times 10^4/\mu\text{L}$. Her renal function was also normal with 0.6 mg/dL of serum creatinine. She was negative for HCV-Ab or HBsAg. The operative time was 192 minutes and total blood loss was 486 g. Pringle maneuver could not be performed due to her history of multiple hepatectomies. Maximum tumor size was 2.5 cm and the number of tumors was three. Pathological analysis revealed F0 fibrosis and A1 inflammation of background liver. Her postoperative course was good without any complications.

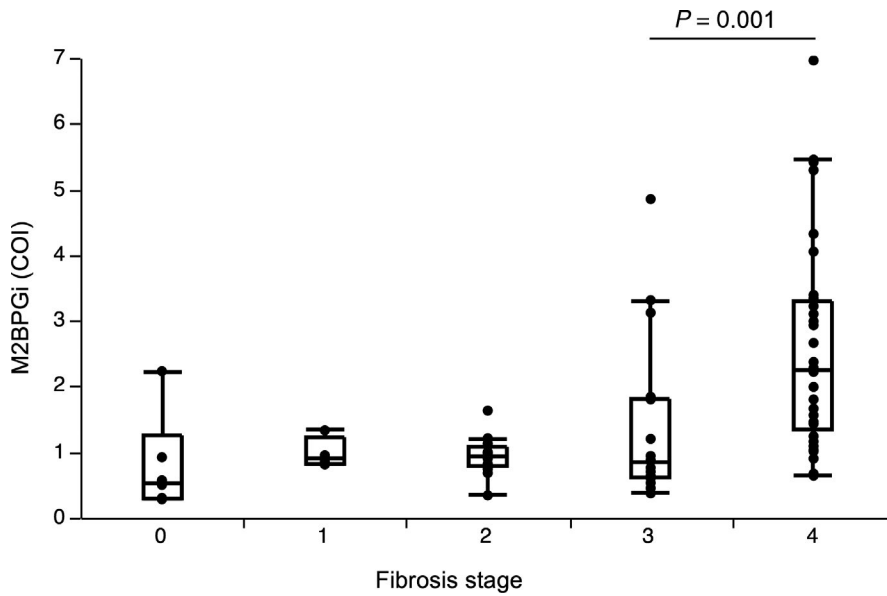


FIGURE 1 Mac-2 binding protein glycosylation isomer (M2BPGi) values for each liver fibrosis stage

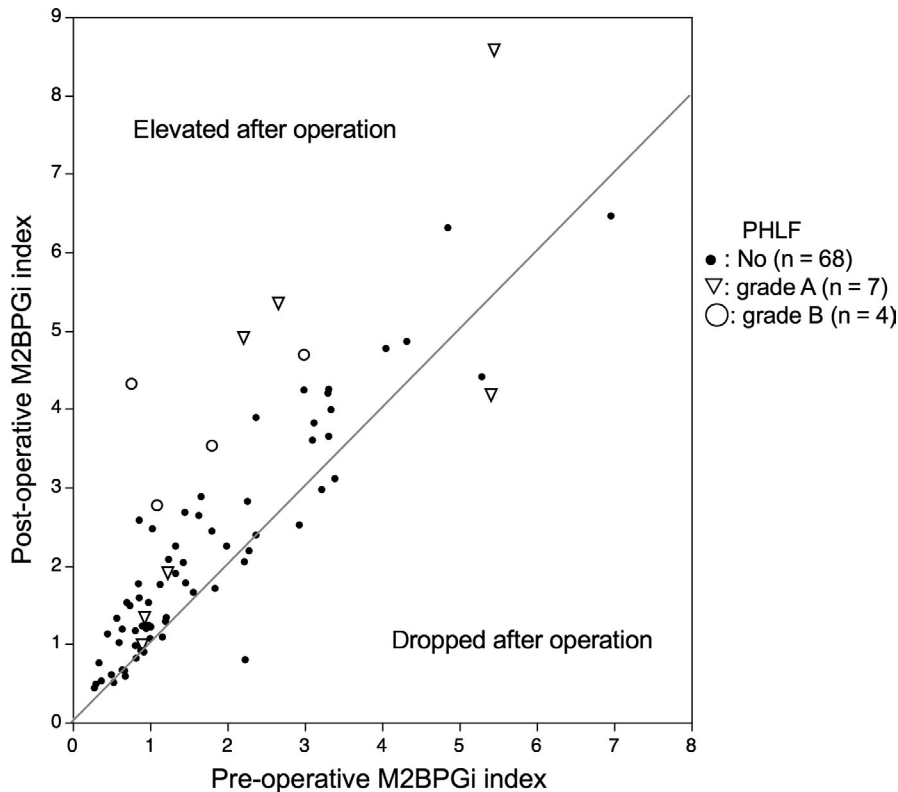


FIGURE 2 Correlation between pre- and postoperative Mac-2 binding protein glycosylation isomer (M2BPGi)

3.4 | Factors that influence the Δ M2BPGi ratio

Univariate and multivariate analyses of perioperative parameters to predict the value of the Δ M2BPGi ratio were performed. A simple linear regression was calculated to predict the Δ M2BPGi ratio based on each factor as shown in Table 2. A significant regression equation was found for females ($F = 5.31$, $P = 0.024$, $R^2 = 0.05$), creatinine ($F = 5.16$, $P = 0.026$, $R^2 = 0.07$), blood loss ($F = 4.77$, $P = 0.033$,

$R^2 = 0.05$), operative time ($F = 19.3$, $P < 0.001$, $R^2 = 0.19$), total Pringle time ($F = 21.0$, $P < 0.001$, $R^2 = 0.21$), PHLF grade \geq B ($F = 26.3$, $P < 0.001$, $R^2 = 0.24$), complication of Clavien-Dindo Class \geq II ($F = 6.91$, $P = 0.010$, $R^2 = 0.07$), and anatomical liver resection ($F = 5.73$, $P = 0.019$, $R^2 = 0.07$). These eight factors were included in a stepwise procedure (minimum BIC method) to select variables for multiple linear regression analysis. Creatinine, total Pringle time and PHLF grade \geq B were selected, and a multiple linear regression was calculated to predict the Δ M2BPGi

TABLE 2 Univariate and multivariate analyses: risk factors associated with increased post/preoperative M2BPGi ratio (n = 79)

Factors	Univariate analysis			Multivariate analysis		
	B	SE B	β	B	SE B	β
Sex, female	-0.19	0.08	-0.25*	NA		
Age	<-0.001	0.006	-0.01			
HCV	0.08	0.08	0.11			
nonBnonC	-0.05	0.08	-0.07			
Creatinine (mg/dL)	0.30	0.13	0.26*	0.28	0.11	0.24*
Child-Pugh score	-0.04	0.22	-0.02			
FIB-4 index	-0.01	0.03	-0.04			
Tumor size (cm)	-0.02	0.04	-0.02			
Single tumor	0.14	0.09	0.18			
Liver cirrhosis (F4)	-0.12	0.08	-0.18			
Blood loss (mL)	<0.001	<0.001	0.24*	NA		
Operative time (min)	0.003	<0.001	0.45***	NA		
Blood transfusion	-0.25	0.17	-0.16			
Total Pringle time (min)	0.007	0.001	0.47***	0.005	0.001	0.31**
PHLF grade \geq B	-0.77	0.15	-0.40***	-0.66	0.15	-0.43***
Clavien-Dindo class \geq II	-0.26	0.10	-0.29*	NA		
Anatomical resection	-0.18	0.08	-0.26*			
The number of days Operation—Check of postoperative M2BPGi	-0.03	0.03	-0.11			

Abbreviations: HCV, hepatitis C virus; NA, not available; PHLF, post-hepatectomy liver failure; SE, standard error.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

ratio based on these three factors. A significant regression equation was found ($F = 17.1, P < 0.0001$) where $R^2 = 0.40$. The patient predicted Δ M2BPGi ratio = $1.536 + 0.0054 \times$ total Pringle time (minutes) + $0.2760 \times$ creatinine (mg/dL) + $0.656 \times$ PHLF grade \geq B, where PHLF grade \geq B was coded as 1 = Yes, -1 = No. Creatinine ($P = 0.013$), total Pringle time ($P = 0.002$) and PHLF grade \geq B ($P < 0.001$) were all significant predictors of the Δ M2BPGi ratio.

We evaluated the association between Δ M2BPGi ratio and total Pringle time in more detail (Figure 3). The total Pringle time was weakly correlated to Δ M2BPGi ratio ($R^2 = 0.23, P < 0.001$).

3.5 | Relationship between PHLF and serologic fibrosis markers

The mean values of the Δ M2BPGi ratio were 1.37 ± 0.07 , 1.52 ± 0.22 , and 2.94 ± 0.30 for PHLF grade 0, grade A, and grade B, respectively, resulting in statistically significant differences by the Kruskal-Wallis test ($P = 0.022$, Figure 4). Differences between the paired stages were significant between grades 0 and B ($P = 0.008$; Wilcoxon rank-sum test). We examined relationships between PHLF and the other fibrosis markers. We also introduced the Δ Hyaluronic acid ratio ($=$ Hyaluronic acid_{after}

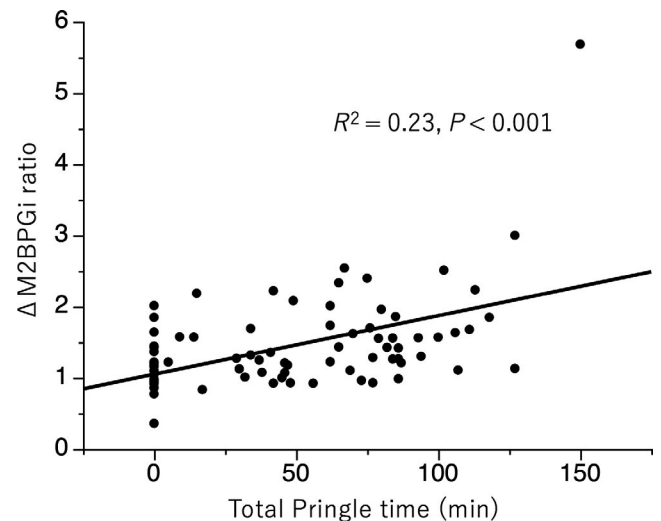


FIGURE 3 Relationship between Δ M2BPGi ratio and total Pringle time

operation/Hyaluronic acid_{before operation}), Δ 4COL7S ratio ($=4COL7S_{after operation}/4COL7S_{before operation}$), and Δ Plt ratio ($=Plt_{after operation}/Plt_{before operation}$) to determine changes in the value around the time of operation. The mean values were as follows. Δ Hyaluronic

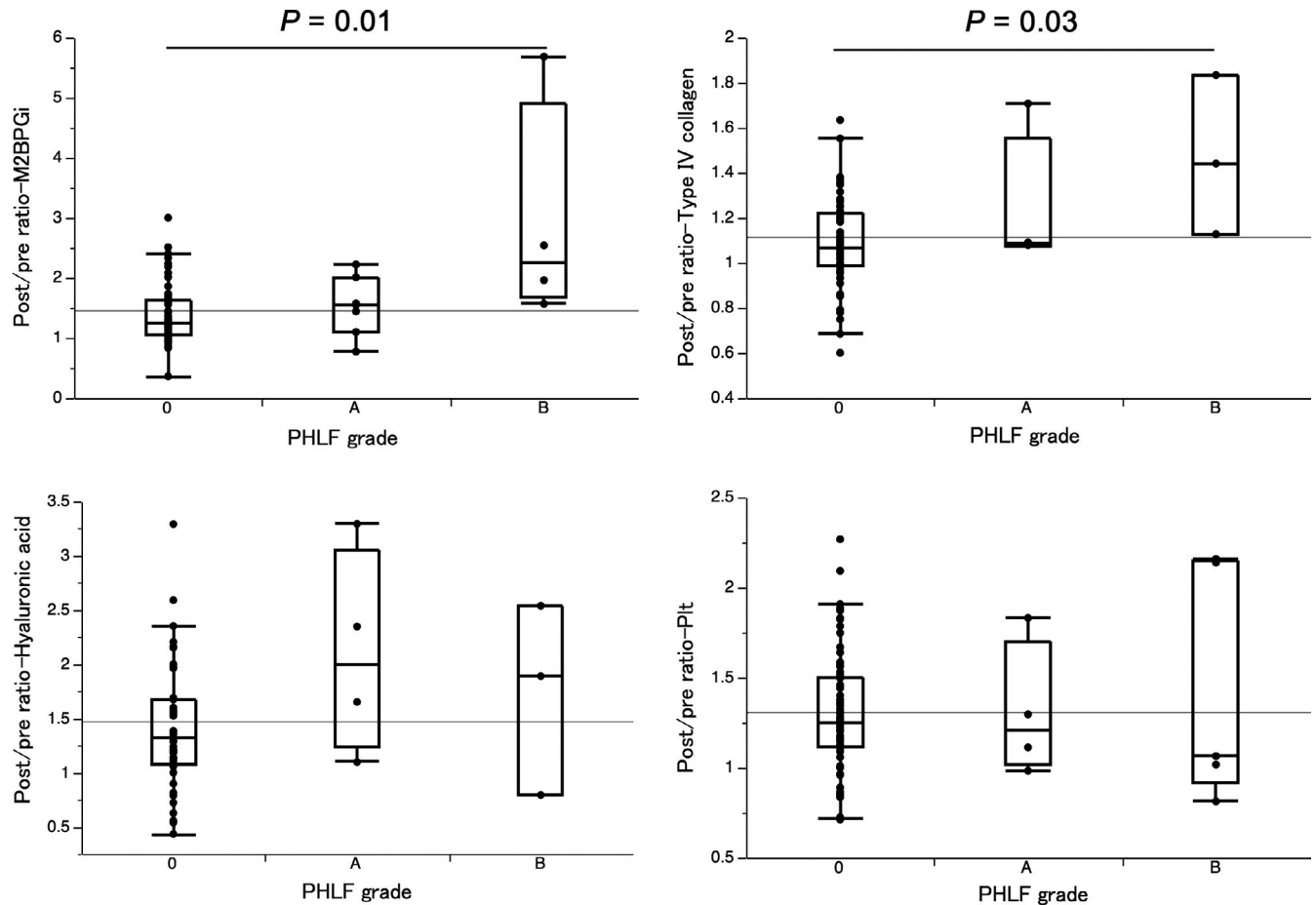


FIGURE 4 Relationship between post-hepatectomy liver failure and serologic fibrosis markers

acid ratio: 1.41 ± 0.08 , 1.88 ± 0.27 , 1.74 ± 0.35 ; $\Delta 4\text{COL7S}$ ratio: 1.09 ± 0.03 , 1.16 ± 0.09 , 1.47 ± 0.12 ; and ΔPlt ratio: 1.30 ± 0.04 , 1.16 ± 0.13 , 1.53 ± 0.18 , for PHLF grade 0, grade A, and grade B, respectively. None of these demonstrated a statistically significant difference by Kruskal-Wallis test. However, differences in the $\Delta 4\text{COL7S}$ ratio between the paired PHLF stages were significant between grades 0 and B ($P = 0.033$; Wilcoxon rank-sum test).

4 | DISCUSSION

The present study is the first to investigate predictive factors for the elevation of M2BPGi after liver resection. Contrary to our expectations, the M2BPGi values were elevated in 80% of all cases even approximately 1 month after liver resection. Furthermore, the factors that influenced the elevation of M2BPGi after liver resection were preoperative creatinine, PHLF grade \geq B and total Pringle time. These observations confirm the previous suggestion that M2BPGi is likely to reflect other factors not limited to liver fibrosis.¹³

Bekki et al¹⁶ reported that hepatic stellate cells (HSCs) were the source of M2BPGi in subpopulations of liver-derived cells. In addition, M2BPGi levels reflected the activation of HSCs during the progression of liver fibrosis.¹⁶ This may explain the rapid decrease of M2BPGi levels

after patients with hepatitis C achieved a sustained virus response.¹⁷ Acute liver failure¹⁸ and ischemia-reperfusion¹⁹ were reported to be associated with HSC activation. Following liver injury, HSCs become activated, trans-differentiating from vitamin A-storing cells to myofibroblasts, which are proliferative, contractile, inflammatory, and chemotactic, and which are characterized by enhanced extracellular matrix production.²⁰ Activated HSCs in these situations may have a high potential to secrete M2BPGi. Indeed, it was reported that M2BPGi was increased in liver transplant patients with acute cellular rejection, even when fibrosis was absent.²¹ Furthermore, Morio et al¹⁴ reported that serum M2BPGi values were associated with clinical outcomes such as acute liver failure, development of hepatic coma, liver transplant, and death, suggesting that M2BPGi might reflect the severity of liver injury. In this study, the ΔM2BPGi ratio increased with advancing PHLF grade, which confirmed the previous study results. Liver resection with a longer total Pringle time causes greater ischemia-reperfusion injury in the liver. Thus, prolonged total Pringle time and PHLF were likely to be associated with the activation of HSCs and secretion of M2BPGi, which continued for at least 1 month after liver resection. Furthermore, a recent study reported that total Pringle time was associated with PHLF (Figure 5).²²

The current study also showed that the elevation of the postoperative value of M2BPGi was associated with preoperative creatinine. Few reports have referred to the relationship between M2BPGi

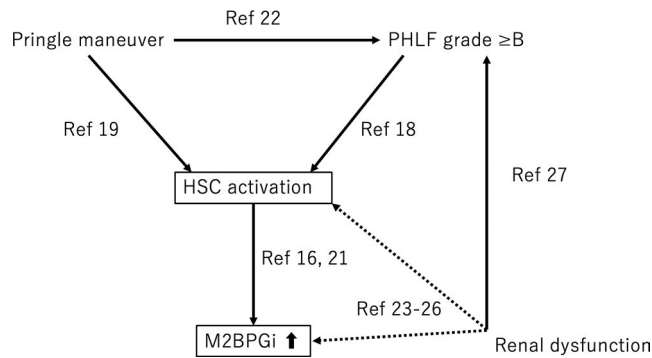


FIGURE 5 Summary of discussion why three factors influence the postoperative elevation of Mac-2 binding protein glycosylation isomer (M2BPGi)

and renal function. Okada et al²³ reported elevated M2BPGi was associated with a decreased estimated glomerular filtration rate in chronic heart failure patients with abnormal liver function. Previous reports demonstrated that tumor necrosis factor- α and interferon- γ can increase M2BPGi expression in fibroblasts.^{24,25} Patients with end-stage renal failure were in systemic inflammatory status, as evidenced by increased levels of cytokines such as interleukin-6 and tumor necrosis factor- α .²⁶ Thus, patients with renal failure might have a tendency to increase M2BPGi expression. In addition, renal failure was also reported to be a risk factor for PHLF (Figure 5).²⁷

We had one patient whose M2BPGi markedly dropped after liver resection. Given her background liver was F0 fibrosis, her preoperative M2BPGi might be accidentally high. Further, none of the three factors, creatinine, PHLF or total Pringle time, were found in her. These combinations might be related to postoperative decrease of M2BPGi.

In this study, we examined M2BPGi values approximately 1 month after liver resection. Morio et al reported that serum M2BPGi values were increased in patients with acute liver injury and decreased following recovery. They defined “recovery” as a normalized serum aminotransferase value. The liver function of patients with PHLF in this study was damaged compared with patients without PHLF at 1 month after liver resection (data not shown), although serum aminotransferase values had normalized at that time. The M2BPGi value of patients with PHLF might decrease to the preoperative level thereafter. Thus, a longer follow up is needed to confirm this.

Why different serologic fibrosis markers exhibit different behaviors after liver resection is unclear. In our study cohort, the Δ 4COL7S ratio exhibited a similar tendency to the Δ M2BPGi ratio regarding its relationship with PHLF. Type IV collagen is found primarily in the basal lamina, although the basal lamina comprised of type IV collagen appeared around the liver sinusoids after liver injury.²⁸ Serum levels of 4COL7S, which has greater sensitivity and specificity for the detection of cirrhosis than type IV collagen, was increased abruptly following acute liver injury.²⁹ It was also reported that type IV collagen accumulated in HSCs during acute viral hepatitis.²⁷ Thus, the elevation of 4COL7S values after PHLF is reasonable and might reflect the activation of HSCs. Although hyaluronic acid is mostly secreted by HSCs,³⁰ hyaluronic acid exhibited a different tendency from M2BPGi regarding its relationship with PHLF.³¹ Further study is required to confirm this.

The Δ M2BPGi ratio was significantly influenced by postoperative complications, such as complications of Clavien-Dindo Class II or more and PHLF in the single linear regression. Due to short observation periods, we could not evaluate the impact of Δ M2BPGi ratio to patients’ prognosis. It has been reported that post-hepatectomy complications were predictive of a worse overall survival in patients with HCC.³² Thus, Δ M2BPGi ratio might be associated with long-term outcomes of patients who underwent liver resection.

A major limitation of this study was its observational design, which was exploratory in nature. The small subject number of the study and its single-center-based design limited the power of the explanation of results. Furthermore, the number of days after liver resection to postoperative serum sampling differed by individual. To minimize the influence of these factors, we excluded patients whose M2BPGi were measured more than 1 month after liver resection. We also confirmed that the Δ M2BPGi ratio was less affected by the number of days between operation and serum sampling by simple linear regression (Table 2). Finally, we did not determine the timely elevation of M2BPGi values during PHLF or liver resection because of the study design. Therefore, we should interpret the results of this study as predictors for the elevation of M2BPGi value at 1 month after liver resection, and not for any other time points.

In conclusion, preoperative creatinine, PHLF grade \geq B and total Pringle time were associated with the elevation of M2BPGi 1 month after liver resection. These observations emphasize the previous suggestion that M2BPGi is likely to reflect liver damage, liver inflammation, and renal function not limited to liver fibrosis.

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DISCLOSURE

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REFERENCES

- Kuno A, Ikehara Y, Tanaka Y, Ito K, Matsuda A, Sekiya S, et al. A serum "sweet-doughnut" protein facilitates fibrosis evaluation and therapy assessment in patients with viral hepatitis. *Sci Rep*. 2013;3:1065.
- Yamasaki K, Tateyama M, Abiru S, Komori A, Nagaoka S, Saeki A, et al. Elevated serum levels of Wisteria floribunda agglutinin-positive human Mac-2 binding protein predict the development of hepatocellular carcinoma in hepatitis C patients. *Hepatology*. 2014;60(5):1563–70.
- Xu H, Kong W, Liu L, Chi X, Wang X, Wu R, et al. Accuracy of M2BPGi, compared with Fibro Scan®, in analysis of liver fibrosis in patients with hepatitis C. *BMC Gastroenterol*. 2017;17(1):62.
- Zou X, Zhu MY, Yu DM, Li W, Zhang DH, Lu FJ, et al. Serum WFA + -M2BP levels for evaluation of early stages of liver fibrosis in patients with chronic hepatitis B virus infection. *Liver Int*. 2017;37(1):35–44.
- Ishii A, Nishikawa H, Enomoto H, Iwata Y, Kishino K, Shimono Y, et al. Clinical implications of serum Wisteria floribunda agglutinin-positive Mac-2-binding protein in treatment-naïve chronic hepatitis B. *Hepato Res*. 2017;47(2):204–15.
- Umemura T, Joshita S, Sekiguchi T, Usami Y, Shibata S, Kimura T, et al. Serum Wisteria floribunda agglutinin-positive Mac-2-binding protein level predicts liver fibrosis and prognosis in primary biliary cirrhosis. *Am J Gastroenterol*. 2015;110(6):857–64.
- Nishikawa H, Enomoto H, Iwata Y, Hasegawa K, Nakano C, Takata R, et al. Impact of serum Wisteria floribunda agglutinin positive Mac-2-binding protein and serum interferon- γ -inducible protein-10 in primary biliary cirrhosis. *Hepato Res*. 2016;46(6):575–83.
- Yamada N, Sanada Y, Tashiro M, Hirata Y, Okada N, Ihara Y, et al. Serum Mac-2 binding protein glycosylation isomer predicts grade F4 liver fibrosis in patients with biliary atresia. *J Gastroenterol*. 2017;52(2):245–52.
- Nishikawa H, Enomoto H, Iwata Y, Hasegawa K, Nakano C, Takata R, et al. Clinical significance of serum Wisteria floribunda agglutinin positive Mac-2-binding protein level and high-sensitivity C-reactive protein concentration in autoimmune hepatitis. *Hepato Res*. 2016;46(7):613–21.
- Abe M, Miyake T, Kuno A, Imai Y, Sawai Y, Hino K, et al. Association between Wisteria floribunda agglutinin-positive Mac-2 binding protein and the fibrosis stage of non-alcoholic fatty liver disease. *J Gastroenterol*. 2015;50(7):776–84.
- Mizuno M, Shima T, Oya H, Mitsumoto Y, Mizuno C, Isoda S, et al. Classification of patients with non-alcoholic fatty liver disease using rapid immunoassay of serum type IV collagen compared with liver histology and other fibrosis markers. *Hepato Res*. 2017;47(2):216–25.
- Nishikawa H, Enomoto H, Iwata Y, Kishino K, Shimono Y, Hasegawa K, et al. Clinical significance of serum Wisteria floribunda agglutinin positive Mac-2-binding protein level in non-alcoholic steatohepatitis. *Hepato Res*. 2016;46(12):1194–202.
- Nagata H, Nakagawa M, Nishimura-Sakurai Y, Asano Y, Tsunoda T, Miyoshi M, et al. Serial measurement of Wisteria floribunda agglutinin positive Mac-2-binding protein is useful for predicting liver fibrosis and the development of hepatocellular carcinoma in chronic hepatitis C patients treated with IFN-based and IFN-free therapy. *Hepato Int*. 2016;10(6):956–64.
- Morio K, Imamura M, Daijo K, Teraoka Y, Honda F, Nakamura Y, et al. Wisteria floribunda agglutinin positive Mac-2-binding protein level increases in patients with acute liver injury. *J Gastroenterol*. 2017;52(12):1252–7.
- Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011;149(5):713–24.
- Bekki Y, Yoshizumi T, Shimoda S, Itoh S, Harimoto N, Ikegami T, et al. Hepatic stellate cells secreting WFA + -M2BP: its role in biological interactions with Kupffer cells. *J Gastroenterol Hepatol*. 2017;32(7):1387–93.
- Shirabe K, Bekki Y, Gantumur D, Araki K, Ishii N, Kuno A, et al. Mac-2 binding protein glycan isomer (M2BPGi) is a new serum biomarker for assessing liver fibrosis: more than a biomarker of liver fibrosis. *J Gastroenterol*. 2018;53(7):819–26.
- Dechêne A, Sowa JP, Gieseler RK, Jochum C, Bechmann LP, El Fouly A, et al. Acute liver failure is associated with elevated liver stiffness and hepatic stellate cell activation. *Hepatology*. 2010;52(3):1008–16.
- Reifart J, Rentsch M, Mende K, Coletti R, Sobocan M, Thasler WE, et al. Modulating CD4 + T cell migration in the postischemic liver: hepatic stellate cells as new therapeutic target? *Transplantation*. 2015;99(1):41–7.
- Tsuchida T, Friedman SL. Mechanisms of hepatic stellate cell activation. *Nat Rev Gastroenterol Hepatol*. 2017;14(7):397–411.
- Yamada N, Katano T, Hirata Y, Okada N, Sanada Y, Ihara Y, et al. Serum Mac-2 binding protein glycosylation isomer predicts the activation of hepatic stellate cells after liver transplantation. *J Gastroenterol Hepatol*. 2019;34(2):418–24.
- Hester CA, El Mokdad A, Mansour JC, Porembka MR, Yopp AC, Zeh HJ 3rd, et al. Current pattern of use and impact of Pringle maneuver in liver resections in the United States. *J Surg Res*. 2019;239:253–60.
- Okada A, Kanzaki H, Hamatani Y, Takashio S, Takahama H, Amaki M, et al. Increased serum Wisteria floribunda agglutinin positive Mac-2 binding protein (Mac-2 binding protein glycosylation isomer) in chronic heart failure: a pilot study. *Heart Vessels*. 2018;33(4):385–92.
- Kong W, Li S, Longaker MT, Lorenz HP. Cyclophilin C-associated protein is up-regulated during wound healing. *J Cell Physiol*. 2007;210(1):153–60.
- Kong W, Lin BW, Li S, Longaker MT, Lorenz HP. Cyclophilin C-associated protein/Mac-2 binding protein colocalizes with calnexin and regulates the expression of tissue transglutaminase. *J Cell Physiol*. 2010;223(1):151–7.
- Kaysen GA. The microinflammatory state in uremia: causes and potential consequences. *J Am Soc Nephrol*. 2001;12(7):1549–57.
- Sugiura T, Dohi Y, Takase H, et al. Serum levels of Mac-2 binding protein increase with cardiovascular risk and reflect silent atherosclerosis. *Atherosclerosis*. 2016;251:192–6.
- Wiggans MG, Shahtahmassebi G, Bowles MJ, Aroori S, Stell DA. Renal dysfunction is an independent risk factor for mortality after liver resection and the main determinant of outcome in posthepatectomy liver failure. *HPB Surg*. 2013;2013:875367.
- Friedman SL. Liver fibrosis – from bench to bedside. *J Hepatol*. 2003;38(Suppl 1):S38–53.
- Suou T, Yamada S, Kobayashi J, et al. Changes of serum 7S fragment of type IV collagen and N-terminal propeptide of type III procollagen after transcatheter arterial embolization as a model of acute liver injury. *Hepatology*. 1993;18(4):809–15.
- Deaciuc IV, Bagby GJ, Lang CH, Spitzer JJ. Hyaluronic acid uptake by the isolated, perfused rat liver: an index of hepatic sinusoidal endothelial cell function. *Hepatology*. 1993;17(2):266–72.
- Harimoto N, Shirabe K, Ikegami T, Yoshizumi T, Maeda T, Kajiyama K, et al. Postoperative complications are predictive of poor prognosis in hepatocellular carcinoma. *J Surg Res*. 2015;199(2):470–7.

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