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RESEARCH ARTICLE

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Serum M2BPGi level is a novel predictive biomarker for the responses to pegylated interferon-α treatment in HBeAg-positive chronic hepatitis B patients

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Serum Mac-2-binding protein glycosylation isomer (M2BPGi) level was found to be a useful prognostic marker for hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB) patients treated with nucleoside/nucleotide analogs (NUCs) therapy, and the aim of our study is to evaluate the clinical implementation of M2BPGi level in the prediction of antiviral responses to pegylated-interferon-α (PEG-IFN-α) treatment in HBeAg-positive CHB patients. Ninety-six CHB patients who received PEG-IFN-α treatment for at least 48 weeks were recruited. The serum M2BPGi, alanine aminotransferase (ALT), hepatitis B surface antigen (HBsAg), HBeAg, and HBV DNA levels at baseline, weeks 4, 12, and 24 after PEG-IFN-α treatment were determined and their associations with antiviral responses were evaluated and the virological response (VR) rate and serological response (SR) rate after 48 weeks of treatment were 65.6% and 35.4%, respectively. Baseline serum M2BPGi level was significantly different between VR and non-VR ($P = 0.002$) or SR and non-SR groups ($P = 0.012$). Multivariate analyses suggested that baseline serum M2BPGi level was independently associated with VR and SR of PEG-IFN-α treatment at week 48. The area under the ROC curve (AUC) of baseline M2BPGi was 0.682 in predicting VR, which was superior to HBsAg (AUC = 0.566) or HBV DNA (AUC = 0.567). The AUC of baseline M2BPGi in predicting SR was 0.655, which was also higher than that of HBsAg (AUC = 0.548) or HBV DNA (AUC = 0.583). These results suggested that

baseline serum M2BPGi level was a novel predictor of VR and SR for PEG-IFN-α treatment in HBeAg-positive CHB patients.

KEYWORDS
chronic hepatitis B, M2BPGi, pegylated interferon-α, response

1 | INTRODUCTION

There are an estimated 240 million people with chronic hepatitis B virus (HBV) infection globally, and about 650 000 will die due to chronic hepatitis B (CHB) annually.[1] Chronically HBV-infected patients have high risk of developing hepatic decompensation, cirrhosis, and hepatocellular carcinoma (HCC) if they could not receive timely and appropriate treatments.[1,2] Clinical studies have suggested that antiviral treatments may prevent progression to cirrhosis, and reduce the risk of HCC and liver-related deaths[3]; however, the current treatment methods failed to eradicate the virus in majority of CHB patients.

Pegylated interferon-α (PEG-IFN-α), which stimulates the immune responses of the host to HBV, is one of the first-line treatment agents recommended by major liver societies treatment guidelines.[2,4,5] The advantages of PEG-IFN-α therapy including a finite treatment course, a relatively higher hepatitis B e antigen (HBeAg) seroconversion rate in HBeAg-positive patients, sustained virological response (SVR), and a relatively high hepatitis B surface antigen (HBsAg) seroclearance or seroconversion rate.[6,7] However, PEG-IFN-α treatment is expensive, inconvenient for clinical application, less well tolerated, and with limited response rate.[2] Therefore, identifying those patients that are response to PEG-IFN-α therapy will guide the clinical treatment choices. Up to date, many clinical studies have reported that ALT, HBsAg, HBeAg, and HBV DNA levels, the host IL28B genotype and HBV genotype were associated with the responses to PEG-IFN-α therapy in CHB patients.[6,8–13] Meanwhile, the quantitative serum HBsAg at week 12, the decline of serum HBsAg level as well as HBV DNA level at week 24 were also predictive factors for PEG-IFN-α therapy.[14] However, the sensitivity and specificity of these biomarkers are still limited and novel biomarkers are warranted to guide clinical selection of PEG-IFN-α in CHB patients.

Mac-2-binding protein glycosylation isomer (M2BPGi), a glycobiomarker, was firstly reported by Kuno et al as a novel biomarker in assessing the liver fibrosis severity in chronic hepatitis patients.[15] Subsequently, studies reported that M2BPGi level might be a noninvasive marker for the assessment of liver fibrosis in patients with chronic hepatitis C (CHC), CHB, nonalcoholic fatty liver disease (NAFLD), autoimmune hepatitis (AIH), and primary biliary cirrhosis (PBC).[16–20] Recently, Nishikawa et al found that pretreatment M2BPGi level might be a useful predictor for HBeAg loss or seroconversion for HBeAg-positive CHB patients that received the treatment of nucleoside/nucleotide analogs (NUCs).[21] However, the predictive roles of M2BPGi for PEG-IFN-α treatment in CHB patients are still unknown.

Thus, the aim of the current study was to investigate the roles and clinical implementations of M2BPGi level in the prediction of virological response (VR) and serological response (SR) in HBeAg-positive CHB patients receiving PEG-IFN-α treatment in a cohort with Chinese patients.

2 | MATERIALS AND METHODS

2.1 | Patients recruitment

HBeAg-positive CHB patients receiving PEG-IFN-α treatment for at least 48 weeks from 2008 to 2016 at Ruijin Hospital or Huashan Hospital, were retrospectively enrolled in the study. The treatment criteria met the American Association for the Study of Liver Diseases (AASLD) guidelines regarding the prevention and treatment of chronic HBV infection (update 2007).[22] Patients were excluded from the study if they: (1) were with hepatitis C virus (HCV) or hepatitis D virus (HDV) co-infection; (2) had prior antiviral therapy; (3) received immunosuppressive therapy within the preceding 6 months; (4) not have sufficient serum sample. VR was defined as an undetectable HBV DNA level (<500 IU/mL) after 48 weeks of therapy. SR was defined as HBeAg seroconversion after 48 weeks of therapy. All stored samples used in the retrospective study had been approved by the Ethical Committee of Ruijin Hospital.

2.2 | Clinical and laboratory measurement

The whole blood samples were collected using vacuum blood tubes with coagulant and the serum was aliquoted and stored at −80°C until analysis. The blood samples were taken at baseline and 4, 12, and 24 weeks after the PEG-IFN-α treatment. Baseline characteristics including age, sex, and clinical information of the patients were extracted from the medical records. HBV serological biomarkers (HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc) were measured using commercially available enzyme immunoassays (CMIA, Abbott, Chicago, IL) according to the manufacturer's instructions. HBV DNA levels were measured using real-time PCR (PJ Co. Ltd., Shenzhen, China) with the lowest detection level of 500 IU/mL. Serum alanine aminotransferase

(ALT) levels were assessed with an automatic biochemical analyzer AU5800 (Beckman Coulter, Brea, CA) in the clinical laboratory diagnosis center.

2.3 | Non-invasive liver fibrosis assessment algorithm

APRI and FIB-4 were calculated as previously described: APRI = AST (/ULN) × 100/PLT (10^9 L^{-1}),[23] and FIB-4 = age (years) × AST [U L^{-1}]/(PLT [10^9 L^{-1}] × (ALT [U L^{-1}])$^{1/2}$).[24]

2.4 | M2BPGi level measurement

Serum M2BPGi level was directly measured with the HISCL™ M2BPGi™ reagent kit (Sysmex, Kobe, Japan) using an automatic immunoanalyzer HISCL-5000 (Sysmex, Hyogo, Japan) at baseline and at 4, 12, and 24 weeks after starting PEG-IFN α treatment. M2BPGi levels were indexed using the following equation: Cut-off Index (C.O.I.) = ([M2BPGi]sample-[M2BPGi]NC)/([M2BPGi]PC)-[M2BPGi]NC), where [M2BPGi]sample represents the M2BPGi count of the serum sample, PC is positive control, and NC is negative control. The positive control was supplied as a calibration solution preliminarily standardized to yield a C.O.I. of 1.0.

2.5 | Statistical analysis

Continuous variables are presented as median (interquartile range) and compared using the Mann-Whitney *U*-test. Serum HBsAg and HBV DNA levels were transformed into logarithmic scale. The univariate and multivariate logistic regression analyses were performed to identify predictive biomarkers of VR and SR after 48 weeks of PEG-IFN-α treatment. Continuous variable were categorized into two groups according to the median levels and the lower group was recognized as the reference. To evaluate the performance of independent risk factors in predicting VR or SR for PEG-IFN α treatment, the receiver-operating characteristic (ROC) curve analysis was performed and the optimal cut-off values were obtained from the

TABLE 1 Baseline characteristics of the recruited patients in the current study

	Variables	Responder	Non-responder	*P*-value
Virological response	*N*[a]	63 (65.6%)	33 (34.4%)	
	Age (years)[b]	29.00 (27.00-34.00)	29.00 (26.50-37.00)	0.985
	Gender[a]			
	Male	44 (69.84%)	24 (72.73%)	0.817
	Female	19 (30.16%)	9 (27.27%)	
	HBsAg (Log_{10} IU · mL^{-1})[b]	3.78 (3.31-4.32)	4.08 (3.65-4.30)	0.193
	HBeAg (S/CO)[b]	424.62 (31.13-1279.45)	1123.00 (656.13-1386.22)	**0.004**
	HBV DNA(Log_{10} IU · mL^{-1})[b]	7.23 (5.76-8.23)	7.48 (6.69-8.20)	0.218
	ALT (IU/L)[b]	146.00 (96.00-265.00)	121.00 (94.00-190.50)	0.442
	M2BPGi (C.O.I)[b]	1.08 (0.72-1.95)	0.62 (0.44-0.97)	**0.002**
	FIB-4[b]	1.13 (0.80-1.45)	0.86 (0.62-1.38)	0.212
	APRI[b]	1.45 (0.70-1.83)	0.84 (0.59-1.52)	0.289
Serological response	*N*[a]	34 (35.4%)	62 (64.6%)	
	Age (years)[b]	29.00 (26.25-34.25)	30.00 (27.25-34.00)	0.631
	Gender[a]			
	Male	24 (70.59%)	44 (70.97%)	0.969
	Female	10 (29.41%)	18 (29.03%)	
	HBsAg (Log_{10} IU · mL^{-1})[b]	3.71 (3.32-4.06)	4.05 (3.51-4.33)	0.241
	HBeAg (S/CO)[b]	305.00 (15.97-1089.41)	966.00 (228.10-1358.35)	**0.023**
	HBV DNA(Log_{10} IU · mL^{-1})[b]	7.14 (5.78-7.92)	7.48 (6.45-8.22)	0.166
	ALT (IU/L)[b]	144.00 (101.00-246.50)	136.00 (93.00-240.00)	0.906
	M2BPGi (C.O.I)[b]	1.10 (0.80-2.57)	0.82 (0.50-1.34)	**0.012**
	FIB-4[b]	1.09 (0.79-1.69)	1.08 (0.75-1.35)	0.476
	APRI[b]	1.54 (0.75-1.83)	1.01 (0.59-1.74)	0.344

HBsAg, HBV surface antigen; HBeAg, HBV e antigen; ALT, alanine aminotransferase; FIB-4, fibrosis index based on the four factors; APRI, AST-to-PLT-ratio-index; M2BPGi, Mac-2 binding protein glycosylation isomer.

[a]Values are the numbers with percentage in parentheses.

[b]Values are the medians with range interquartile in parentheses.

A *P* value < 0.05 is labeled as bold.

Youden's index. Diagnostic accuracy was expressed as the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the area under the ROC curve (AUC). All analyses were performed using Empower(R) (www.empowerstats.com, X&Y solutions, Inc., Boston, MA) and R (http://www.R-project.org) as well as GraphPad Prism 5 (GraphPad, San Diego, CA). A *P*-value <0.05 at two-sided was considered as statistically significant for all tests.

3 | RESULTS

3.1 | Baseline characteristics of patients

Totally, 96 eligible patients were enrolled in this study. The baseline characteristics of the eligible patients are presented in Table 1. Of them, 68 (70.8%) are men and 28 (29.2%) are women with a median age of 29 years old. After 48 weeks of PEG-INF-α treatment, 63 (65.6%) patients achieved virological response. Thirty-four out of 96 patients (35.4%) showed serological response.

3.2 | Characteristics comparison between patients with or without virological or serological response during PEG-INF-α treatment

Compared to VR patients, those patients with non-VR had significantly lower baseline M2BPGi level (0.62 vs 1.08 C.O.I; $P = 0.002$; Table 1) and higher HBeAg (1123.00 vs 424.62 S/CO; $P = 0.004$; Table 1). No significant difference was noticed for M2BPGi at weeks 4, 12, and 24 after the PEG-INF-α treatment between the non-VR and VR groups (Figure 1 and Supplementary Table S1). Higher HBeAg at week 4 (850.10 vs 39.38 S/CO, $P = 0.026$), week 12 (680.17 S/CO vs 12.90 S/CO $P < 0.001$), and week 24 (228.08 S/CO vs 6.36 S/CO, $P < 0.001$) were noticed in patients with non-VR groups compared to VR groups (Figure 1 and Supplementary Table S1). HBV DNA at weeks 4, 12, and 24 in the non-VR groups were significantly higher than patients in VR groups (Figure 1 and Supplementary Table S1). No significantly differences were noticed for HBsAg, and ALT ($P > 0.05$; Supplementary Table S1) between the non-VR and VR groups for patients received Peg-IFN-α treatment.

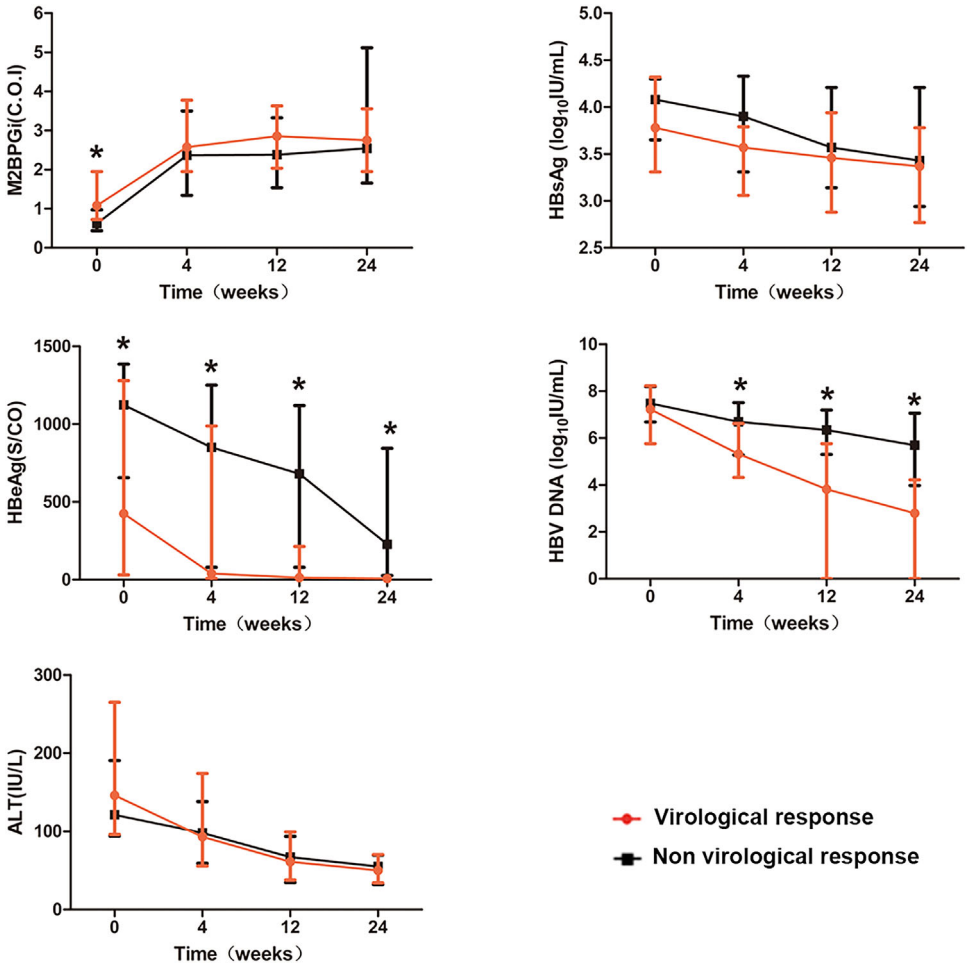

FIGURE 1 Time course changes of M2BPGi, HBsAg, HBeAg, HBV-DNA, and ALT levels in VR and non-VR patients received 48-week Peg-IFN-α treatment. *$P < 0.05$. ●, represents the median value of each parameter in the group with virological response; ▪, represents the median value of each parameter in the group without virological response; the bottom and top of the whiskers represent 25 and 75 percentiles of each parameter. The values in two different groups were compared using the Mann-Whitney *U*-test

Patients in the non-SR group had significant lower baseline M2BPGi level (0.82 vs 1.10 C.O.I; $P = 0.012$) and higher HBeAg (966.00 vs 305.00 C.O.I; $P = 0.023$) compared to SR group (Table 1). Compared to SR group, patients in the non-SR group had significantly higher HBeAg and HBV DNA at weeks 12 and 24; however, the difference was not statistically significant at week 4 after the treatment (Figure 2 and Supplementary Table S1). No significantly differences were noticed in M2BPGi, HBsAg, and ALT between the non-SR and SR groups during the treatment (Figure 2 and Supplementary Table S1).

3.3 | Clinical characteristics factors associated with virological or serological response to Peg-IFN-α treatment

Univariate analysis suggested that baseline HBeAg and M2BPGi levels were significantly associated with VR after 48-week Peg-IFN-α treatment (Table 2). HBeAg as well as HBV-DNA levels at weeks 12 and 24 were associated with VR after the 48-week Peg-IFN-α treatment for CHB patients, but not for M2BPGi or ALT levels at weeks 4, 12, and 24 (Supplementary Table S2). After adjusting for HBsAg and ALT, the multivariate analyses suggested that baseline M2BPGi (>0.94 vs ≤0.94, adjusted OR = 4.65, 95% CI = 1.57-13.77, $P = 0.0056$; Table 3) was independently associated with VR. After adjusting for M2BPGi and HBsAg, the multivariate analyses suggested that baseline HBeAg (>695.30 vs ≦695.30, adjusted OR = 0.27, 95%CI = 0.09-0.81, $P = 0.0194$; Table 3) was independently associated with VR.

Univariate analyses suggested that baseline M2BPGi level and HBeAg were significantly associated with SR (Table 2). After adjusting for HBsAg and ALT levels, the multivariate analysis indicated a statistically marginal association between the baseline M2BPGi level and SR (>0.94 vs ≤0.94, adjusted OR = 2.70, 95%CI = 0.98-7.46, $P = 0.056$, Table 3). After adjusting for M2BPGi, the multivariate analyses suggested that baseline HBeAg (>695.30 vs ≦695.30, adjusted OR = 0.47, 95%CI = 0.18-1.21, $P = 0.1182$; Table 3) was not independently associated with SR.

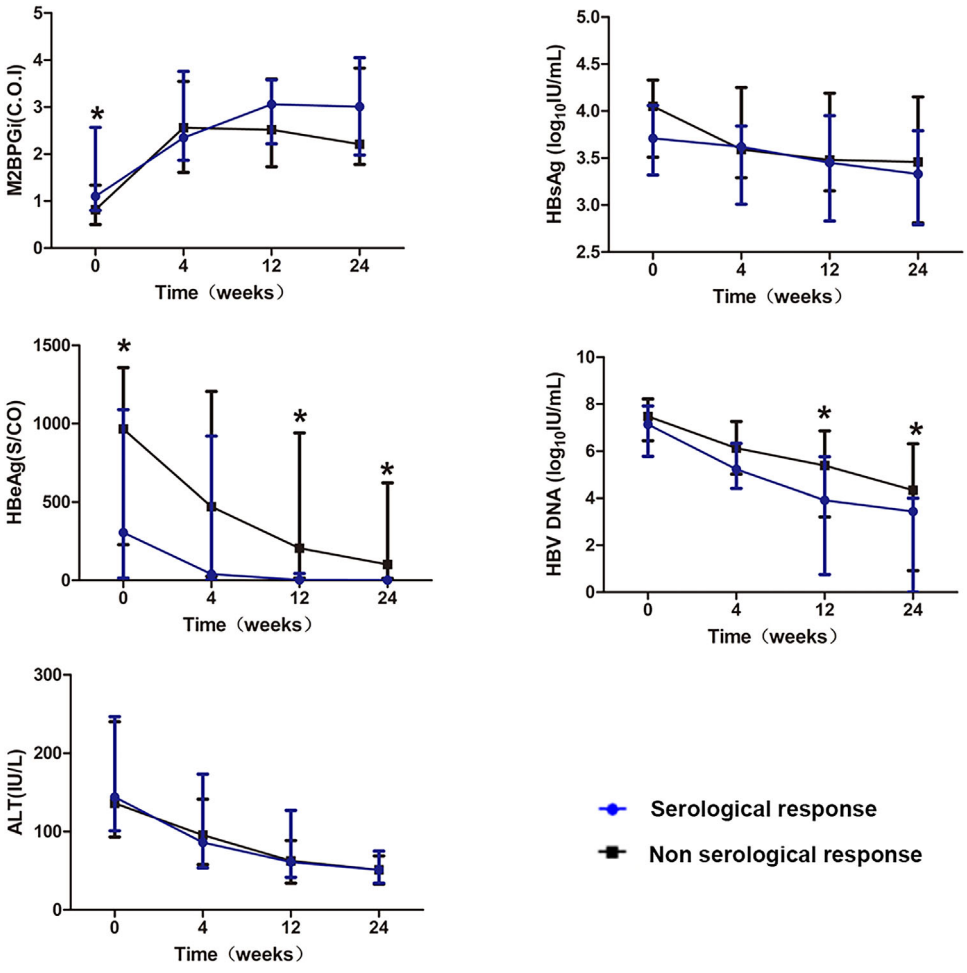

FIGURE 2 The time change of M2BPGi, HBsAg, HBeAg, HBV-DNA, and ALT levels in SR and non-SR patients received 48-week Peg-IFN-α treatment. *$P < 0.05$. ●, represents the median value of each parameter in the group with serological response; ▪, represents the median value of each parameter in the group without serological response; the bottom and top of the whiskers represent 25 and 75 percentiles of each parameter. The values in two different groups were compared using the Mann-Whitney *U*-test

TABLE 2 Univariate analysis of baseline characteristics and their associations with virological and serological responses in CHB patients received 48-week Peg-IFN-α treatment

	Virological response OR (95% CI)	*P*-value	Serological response OR (95% CI)	*P*-value
Gender				
Female	1.0		1.0	
Male	0.87 (0.34, 2.21)	0.768	0.98 (0.39, 2.46)	0.969
Age				
≦28	1.0		1.0	
>28	1.13 (0.48, 2.69)	0.782	0.79 (0.33, 1.85)	0.582
HBsAg(Log_{10} IU · mL^{-1})				
≦3.86	1.0		1.0	
>3.86	0.48 (0.20, 1.14)	0.097	0.55 (0.23, 1.30)	0.172
HBeAg (S/CO)				
≦695.30	1.0		1.0	
>695.30	0.22 (0.08, 0.58)	**0.002**	0.40 (0.16, 0.98)	**0.046**
HBV DNA (Log_{10} IU · mL^{-1})				
≦7.28	1.0		1.0	
>7.28	0.65 (0.28, 1.52)	0.317	0.56 (0.24, 1.30)	0.176
ALT (IU · L^{-1})				
≦136	1.0		1.0	
>136	2.03 (0.83, 4.95)	0.121	1.10 (0.46, 2.65)	0.823
M2BPGi (C.O.I)				
≦0.94	1.0		1.0	
>0.94	4.33 (1.73, 10.87)	**0.002**	2.54 (1.07, 6.03)	**0.035**

HBsAg, HBV surface antigen; HBeAg, HBV e antigen; ALT, alanine aminotransferase; M2BPGi, Mac-2 binding protein glycosylation isomer.
Values expressed as odds ratio (OR) and 95% confidence interval (CI).
A *P* value < 0.05 is labeled as bold.

3.4 | Predictive values of baseline M2BPGi levels for VR and SR

With the ROC curves, we compared the predictive performance of baseline serum M2BPGi, HBsAg, and HBV-DNA in predicting the VR and SR to 48-week Peg-IFN-α treatment in CHB patients. The AUC was 0.682 (95%CI = 0.568-0.792) of M2BPGi, which was higher than HBsAg (AUC = 0.566, 95%CI = 0.455-0.693; *P* = 0.084) and HBV DNA (AUC = 0.567, 95%CI = 0.446-0.667; *P* = 0.142) in predicting VR. Based on Youden's index algorithm in the ROC curve, the optimal cut-off value of M2BPGi in predicting VR was 0.69 C.O.I, with sensitivity of 77.8%, specificity of 60.6%, PPV of 79.0%, and NPV of 58.5% (Figure 3 and Supplementary Table S3).

In SR prediction, the AUC was 0.655 (95%CI = 0.544-0.762) of M2BPGi, which was higher than HBsAg (AUC = 0.548, 95% CI = 0.437-0.696; *P* = 0.219) and HBV DNA (AUC = 0.583, 95% CI = 0.444-0.702; *P* = 0.328). Based on Youden's index algorithm, the optimal cut-off value of M2BPGi in SR prediction was 0.89 C.O.I, with sensitivity of 70.6%, specificity of 54.8%, PPV of 46.2%, and NPV of 77.3% (Figure 3 and Supplementary Table S3).

TABLE 3 Multivariate analysis of baseline characteristics and their associations with virological and serological responses in CHB patients received 48-week Peg-IFN-α treatment

	Virological response OR (95%CI)	*P*-value	Serological response OR (95%CI)	*P*-value
M2BPGi(C.O.I)				
≦0.94	1.0		1.0	
>0.94	4.65 (1.57, 13.77)[a]	**0.0056**	2.70 (0.98, 7.46)[a]	0.0557
HBeAg (S/CO)				
≦695.30	1.0		1.0	
>695.30	0.27 (0.09, 0.81)[b]	**0.0194**	0.47 (0.18, 1.21)[c]	0.1182

Values expressed as odds ratio (OR) and 95% confidence interval (CI).
M2BPGi, Mac-2 binding protein glycosylation isomer.
[a]Adjusted for age, baseline HBsAg, and ALT.
[b]Adjusted for baseline HBsAg and M2BPGi.
[c]Adjusted for baseline M2BPGi.
A *P* value < 0.05 is labeled as bold.

4 | DISCUSSION

Peg-IFN-α is one of the two major first-line treatments methods recommended by current clinical practice guidelines for CHB patients.[25] The clinical responses to Peg-IFN-α treatment varied greatly among individuals; however, the underlying mechanisms are largely unknown. Identification of patients who will benefit from this treatment would be of great clinical importance, as it might guide the clinicians to select suitable treatment methods and adjust the therapy methods timely to reduce side effects and the medical costs. HBeAg seroconversion is regarded as one of the most important surrogate indicators to determine the duration and efficacy of antiviral therapy in CHB patients received the antiviral treatments, and it is associated with better long-term clinical prognosis, histological improvement, and increased survival rate.[26,27] In this study, we evaluated the dynamic changes of serum M2BPGi, HBsAg, HBeAg, and HBV DNA in HBeAg-positive CHB patients receiving Peg-IFN-α treatment for 48 weeks and found that baseline serum M2BPGi level was a novel predictive biomarker for VR and SR, which may guide the Peg-IFN-α treatment for CHB patients in future.

M2BP, the Mac-2 binding protein, is an extracellular matrix component secreted by a variety of cells, such as hepatocytes, fibroblasts. M2BP monomers have seven N-glycans and it is involved in pathophysiological process. M2BPGi is a protein that can be recognized by lectin WFA and anti-M2BP antibody, with high specificity. M2BPGi was correlated with ALT, hepatic inflammation and cytokine IP-10 levels,[19,21,28] which suggested that M2BPGi might be associated with host immune activation. It has been reported that serum M2BPGi can be used to evaluate liver fibrosis caused by a variety of etiology, and it was associated with hepatocellular carcinoma (HCC) risk in chronic HBV or HCV patients.[16–20,29,30] Moreover, M2BPGi is also a novel predictive biomarkers to NUCs as

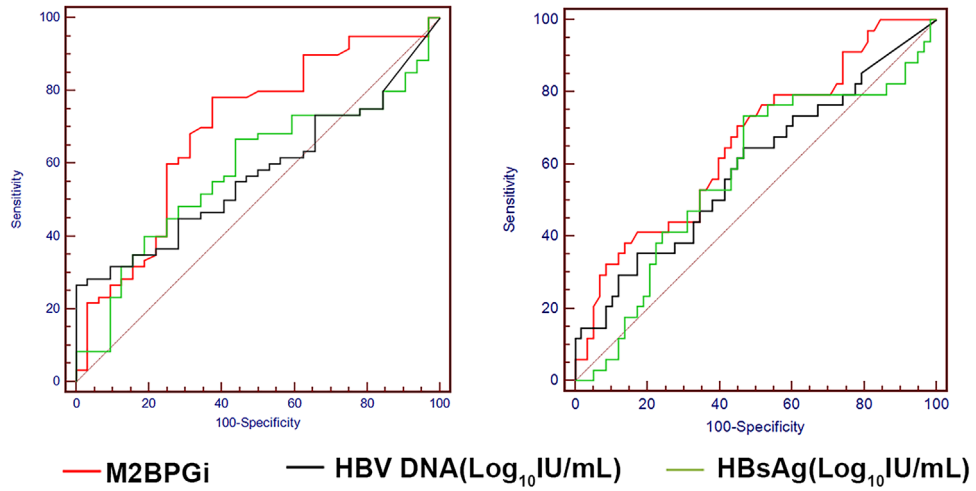

FIGURE 3 The receiver operating characteristics curves of M2BPGi, HBV-DNA, and HBsAg at baseline in predicting antiviral response after 48-week Peg-IFN-α treatment in CHB patients. Left, virological response; right, serological response

suggested by a study performed by Nishikawa et al.[21] However, the values of serum M2BPGi level on virological and serological response for HBeAg-positive CHB patients with Peg-IFN-α therapy had not yet been evaluated. In the current study, we firstly evaluated the predictive abilities of baseline serum M2BPGi in HBeAg-positive CHB patients with Peg-IFN-α therapy. The univariate and multivariate analyses suggested that serum baseline M2BPGi have promising values in predicting the SR and VR responses to those patients receiving Peg-IFN-α therapy. Compared to NUCs, Peg-IFN-α treatment had different mechanisms of action, higher probability to achieve SR and a relatively finite course of treatment. It has been reported that the predictive biomarkers for responses to NUCs and Peg-IFN-α treatment predictors are not exactly the same and the previous results suggested M2BPGi levels might be associated with the host immune status, which may underlie the mechanisms for the association between M2BPGi levels and the clinical responses to NUCs and Peg-IFN-α treatments.

Epidemiological studies have determined other variables that may be associated with VR or SR of CHB patients received the Peg-IFN-α treatment, including sex, age, ALT, HBsAg, HBeAg, and HBV DNA.[31,32] It has been suggested that low HBV-DNA load ($<2 \times 10^8$ IU · mL^{-1}), low HBeAg, high serum ALT levels (>2-5 × ULN) and high hepatic activity score of liver biopsy (at least A2) at baseline are associated with HBeAg seroconversion.[13,14] HBsAg <1500 IU/mL at week 12 after the treatment was a strong predictor of HBeAg seroconversion,[33] while HBsAg levels >20 000 IU/mL or show no HBsAg levels decline at 12 weeks are associated with a low chance of HBeAg seroconversion at week 48.[34] Fried et al reported that a HBV DNA decrease to <20 000 IU/mL at week 12 was associated with a 50% chance of anti-HBe seroconversion, and HBeAg levels at week 24 also had predictive values in predicting the HBeAg seroconversion of patients received the Peg-IFN-α treatment.[14] In the present study, we found 63 (65.6%) reached virological response, and 34 (35.4%) reached serological response out of 96 patients received 48-week of Peg-IFN-α treatment. The response rate was comparable to previous study on the efficacy of Peg-IFN-α treatment. For example, Fried et al[14] reported that the highest rate of HBeAg seroconversion occurred in patients treated with Peg-IFN alfa-2a monotherapy (32%), followed by those treated with Peg-IFN alfa-2a plus lamivudine (27%) and those treated with lamivudine alone (19%) in a study involving 271 HBV-infected HBeAg-positive patients who received Peg-IFN alfa-2a plus treatment for 48 weeks.

We here also monitored the serum kinetics of serum M2BPGi, HBsAg, HBeAg, and HBV-DNA at different time course after the treatment. HBsAg reduced slowly over time, which suggested the difficulty of complete clearance of HBsAg as HBsAg partly reflects the amount of intrahepatic cccDNA levels.[35] HBeAg and HBV DNA showed a rapidly decline after the treatment initiation, suggesting the efficiency of Peg-IFN-α method for CHB patients. The serum M2BPGi was relatively lower before the treatment of Peg-IFN α, and it was gradually increased to a plateau status. We determined the associations between these factors (including sex, age, ALT, HBsAg, HBeAg, HBV DNA, APRI, and FIB-4) and their associations with VR and SR after 48-week Peg-IFN-α treatment. We only identified that HBeAg had predictive values for virological and serological responses. As the results for the associations between these clinical characteristics and the SR or VR to Peg-IFN-α treatment are not always consistent,[34,36–38] more studies are warranted to address their clinical relevance.

We acknowledged that there are several limitations for the current study. First, the study is a retrospective study with a limited sample size. The patients were followed up for a short time and it was not possible to evaluate the sustained responses of the patients after discontinuation of the treatment. Second, the HBV genotype was not determined, which may influence the outcomes for Peg-IFN-α treatment. Previous studies have shown that the HBV genotypes prevalent in Chinese population are mostly genotypes B and C, and genotype B is associated with better responses to interferon therapy

than genotype C.[6] Thus, the HBV genotypes should be taken into consideration to evaluate the associations between the M2BPGi and clinical responses in future. Third, genetic background that might be associated with the responses to Peg-IFN-α treatment was not determined such as the single nucleotide polymorphisms (SNPs) located within IL28B. However, whether these SNPs affect the response to interferon therapy is still controversial in CHB patients.[39,40] Thus, further studies with large number of patients are needed to validate the results.

In conclusion, our current study found that baseline serum M2BPGi has predictive value for the clinical responses of HBeAg-positive chronic hepatitis B patients receiving Peg-IFN-α treatment. More studies with larger sample size are warranted to validate the results and the underlying mechanisms need to be explored.

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CONFLICTS OF INTEREST

The authors declared that they have no competing financial interests.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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