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Clinical Predictors for Neutrophil–to–Lymphocyte Ratio Changes in Patients with Chronic Hepatitis B Receiving Peginterferon Treatment

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Abstract. *Background: A lower neutrophil–to–lymphocyte ratio (NLR) was found to be associated with better clinical outcomes in hepatitis B-related liver cirrhosis and hepatocellular carcinoma. We aimed to identify pre-therapeutic variables capable of predicting NLR changes in patients with hepatitis B receiving peginterferon therapy. Patients and Methods: The baseline clinicopathological data were analyzed to correlate with NLR changes before and 1 year after peginterferon treatment in 71 patients with hepatitis B. Results: Univariate analysis revealed that pre-treatment NLR itself negatively predicted NLR changes following peginterferon treatment (odds ratio(OR)=0.320, p=0.013). Further analysis identified pre-treatment NLR, hemoglobin and hepatitis B surface antigen level as independent predictors for NLR changes (adjusted p=0.028, 0.005, and 0.028, respectively). A predictive score composed of these three factors had an area under the curve of 76.5% (p<0.001). Conclusion: Pretreatment NLR, hemoglobin and hepatitis B surface antigen level in combination, effectively predicted NLR changes following peginterferon treatment.*

Hepatitis B virus (HBV) infection is a global public health issue. There are about 250 million HBV carriers in the world, of whom roughly 600,000 die annually from HBV-related liver disease, including liver cirrhosis and hepatocellular carcinoma (HCC) (1-4). Interferon and nucleos(t)ide analogs are two major classes of antiviral therapies against HBV. Both are capable of reducing the incidence of HCC (5-8). In view of HCC prevention, peginterferon remains superior to nucleos(t)ide analogs (9). One possible reason for this is the emergence of HBV surface antigen truncation mutations, which had increased oncogenic potentials, in patients receiving long-term nucleos(t)ide analogue therapy (9-11) and the other is the immunomodulatory properties of peginterferon, which is believed to exert anticancer effect (12).

One of the major contributing factors for HCC development, recurrence and metastasis is the imbalance of inflammatory response (13-15). Several indicators of systemic inflammation, such as C-reactive protein, neutrophil–to–lymphocyte ratio (NLR), lymphocyte–to–monocyte ratio, platelet–to–lymphocyte ratio (PLR) and modified Glasgow prognostic score have been used for evaluation of inflammatory status. Neutrophils and lymphocytes are the essential components of the tumor-related stroma, and are closely correlated to local inflammation and immune responses (16). Because blood neutrophil and lymphocyte counts are routinely checked during clinical practice, NLR is widely used as a reference for immunological status of the patients (17). Nowadays, a higher NLR has been correlated with poorer prognosis in several malignancies (18-23), including resectable and advanced HCC (24-26). In this way, lower NLR seems to imply a lower risk and better outcome of HCC in chronic HBV-infected patients. We, therefore, hypothesized that the NLR change post peginterferon treatment might provide an explanation for its superior HCC-prevention effect. Searching the literature, there is no study focusing on the change of NLR after peginterferon treatment in chronic hepatitis B patients. In this study, we aimed to clarify this important issue.

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Patients and Methods

Patients. Under the approval of the Chang Gung Medical Foundation Institutional Review Board, we retrieved the clinical data of 123 patients with chronic hepatitis B, who underwent liver biopsy as part of pretreatment evaluations between 2007 and 2009. Of them, 52 patients either did not receive any antiviral treatments or received only nucleos(t)ide analogues therapy. These patients were excluded. The remaining 71 patients were treated with peginterferon and were enrolled into this study. All participants were given written informed consent. Baseline pretreatment data were reviewed, which included age, gender, liver cirrhosis, Ishak histology activity indexes (27), HBV DNA level, HBV e antigen (HBeAg), quantitative HBV surface antigen (HBsAg) level, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, platelet count, hemoglobin (Hb), total white blood cell count (WBC), neutrophil count, lymphocyte count, neutrophil percentage, lymphocyte percentage, NLR, and PLR. Post-treatment data (>1 year after the end of treatment) included total WBC count, neutrophil count, lymphocyte count, neutrophil percentage, lymphocyte percentage, NLR, and PLR. Diagnosis of HCC was made by liver biopsy or aspiration cytology; if tissue-based diagnosis could not be performed due to patients' conditions, dynamic computed tomography and angiography with an alpha-fetoprotein level of >200 ng/ml were used as diagnostic criteria (28, 29). HBV DNA levels were measured by COBAS TaqMan HBV test (Roche Molecular Systems, Branchburg, NJ, USA). Quantitation of the HBsAg level was assessed using the Elecsys HBsAg II assay (Roche Diagnostics, Indianapolis, IN, USA). Patients were followed up for at least 5 years after the pretreatment biopsy.

Antiviral treatments. All enrolled patients were treated with peginterferon alfa-2a (Pegasys, Roche, Basel, Switzerland), including those who were treated with peginterferon monotherapy (n=37) and those who were also treated with nucleos(t)ide analogs before, during, or after the peginterferon therapy (n=34). In HBeAg-positive patients, peginterferon was given for at least 6 months, and in HBeAg-negative patients, peginterferon was given for at least 1 year. The treatments were administered according to Asian Pacific Association for the Study of the Liver (APASL) guidelines (30).

Statistical analysis. Numerical data are presented as mean±standard deviation, while categorical data are expressed as absolute numbers and percentages. Immunological changes after peginterferon treatment were evaluated by paired *t*-test, and shown as mean±standard deviation and *p*-value. Univariate and multivariate analyses were performed by linear regression to identify independent factors for post-treatment NLR. The results are presented as regression coefficient (B), with 95% confidence interval (CI) and *p*-value. We used logistic regression to evaluate clinical factors associated with binary NLR change. In this part, if a continuous variable had a *p*-value of less than 0.3, we modified it into a dichotomous variable for further analysis by use of the optimal cutoff points decided by receiver operating characteristic (ROC) curves with Youden index for better clinical application. The results are presented as odd ratios (OR), with 95% CI and *p*-value. The results were considered to indicate a statistically significant difference when *p*-value less than 0.05. All statistical calculations were performed using SPSS software, version 21 (IBM, Armonk, NY, USA).

Table I. *Baseline characteristics*.

Characteristic	Value (n=71)
Age, years	39.14±10.33
Gender, n (%)	
Male	60 (84.5%)
Female	11 (15.5%)
Cirrhosis, n (%)	16 (22.5%)
Ishak histology activity index	3.01±1.43
Piecemeal necrosis (score>1)	12 (16.9%)
Confluent necrosis (score>0)	7 (9.9%)
Focal (spotty) lytic necrosis, apoptosis, and focal inflammation (score>2)	15 (21.1%)
Portal inflammation (score>2)	30 (42.3%)
Viral serological analysis	
HBV DNA load, $\log_{10}$ IU/ml	7.09±1.34
HBeAg positive	49 (69%)
HBsAg level, $\log_{10}$ IU/ml	3.65±0.88
Other laoratory analysis	
ALT, IU/l	157.41±133.05
AST, IU/l	91.64±79.63
Bilirubin, mg/dl	0.91±0.29
Platelet count, ×1000/mm^3	198.25±43.37
Hemoglobin, g/dl	15.12±1.37
Pre-treatment immunological status	
Total white blood cell count, /μl	5697.18±1541.98
Neutophil count, /μl	2919.82±1005.35
Lymphocyte count, /μl	2209.55±766.86
Neutrophil percentage,%	51.05±8.92
Lymphocyte percentage,%	38.91±8.57
NLR	1.44±0.63
PLR	100.00±38.22
Post-treatment immunological status	
Total white blood cell count, /μl	5660.00±1301.44
Neutophil count, /μl	2976.69±846.47
Lymphocyte count, /μl	2114.87±732.35
Neutrophil percentage,%	52.92±9.36
Lymphocyte percentage,%	37.32±8.70
NLR	1.58±0.78
PLR	102.14±46.07

Data are mean value±standard deviation or number (%). HBV, Hepatitis B virus, HBeAg, hepatitis B virus e antigen; HBsAg, hepatitis B virus surface antigen; ALT, alanine transaminase; AST, aspartate transaminase; NLR, neutrophil–to–lymphocyte ratio; PLR, platelet–to–lymphocyte ratio.

Results

Basic clinicopathological characteristics. This study enrolled 71 patients who received pre-treatment clinical evaluation including liver biopsy before peginterferon treatment. Post-treatment WBC differential count data were also collected. Baseline clinicopathological characteristics and post-treatment WBC differential count data are shown in Table I. As expected, male patients were predominant (male/female= 84.5%/15.5%). There were 15 (21.1%) patients with liver cirrhosis. Ishak histology activity index was 3.01±1.43. In view of the virological data, 49 (69%) patients were positive for HBeAg;

Table II. *Changes of white blood cell (WBC) differential counts before and after peginterferon treatment.*

Parameter	Pre-treatment	Post-treatment	Difference	*p*-Value
Total WBC, /μl	5697.18±1541.98	5660.00±1301.44	−60.00±1422.84	0.725
Neutophil count, /μl	2919.82±1005.35	2976.69±846.47	56.87±944.41	0.613
Lymphocyte count, /μl	2209.55±766.86	2114.87±732.35	−94.67±702.97	0.260
Neutrophil percentage,%	51.05±8.92	52.92±9.36	1.88±8.82	0.077
Lymphocyte percentage,%	38.91±8.57	37.32±8.70	−1.58±8.43	0.118
NLR	1.44±0.63	1.58±0.78	0.14±0.73	0.103
PLR	100.00±38.22	102.14±46.07	2.136±44.76	0.689

Data are presented as mean value±standard deviation. NLR, Neutrophil–to–lymphocyte ratio; PLR, platelet–to–lymphocyte ratio.

the mean±SD $\log_{10}$ HBV DNA was 7.09±1.34 IU/ml, and $\log_{10}$ HBsAg was 3.65±0.88 IU/ml. Two (2.8%) patients developed HCC during the later follow-up periods after treatment.

Changes of WBC differential counts between pre-treatment and one year after peginterferon treatment. When the WBC differential counts data were compared for the whole study group, before and one year after peginterferon treatment, no statistical significance was found in total WBC count, neutrophil count, lymphocyte count, neutrophil percentage, lymphocyte percentage, NLR and PLR (Table II). This result indicated that no single directional change of WBC parameters were found after peginterferon treatment.

We further analyzed the factors associated with post-treatment NLR by use of regression analysis (Table III). In univariate regression analysis, age (beta=−0.020; 95% CI=−0.039-0.000; p=0.047) and pre-treatment NLR (beta=0.682; 95% CI=0.277-1.087; p=0.001) were significantly associated with post-treatment NLR. In multivariate regression analysis, only pre-treatment NLR was independently associated with post-treatment NLR (beta=−0.262; 95% CI=−0.445-−0.078; p=0.006). Intriguingly, pre-treatment NLR and post-treatment NLR were negatively correlated.

Clinical parameters associated with NLR changes before and after peginterferon treatment. Because of the interesting finding that the pre-treatment NLR was negatively associated with post-treatment NLR in regression analysis, we subsequently analyzed other clinical factors associated with NLR changes (ΔNLR) before and after peginterferon treatment. When NLR remained the same or increased, ΔNLR would be ≥0, whereas when NLR decreased, ΔNLR would be <0. Logistic regression analysis was, thus, performed accordingly (Table IV).

For better clinical application, when a continuous variable had a value of p<0.3, we also included this variable as a dichotomous variable for further analysis. The cut-off point was decided by a ROC curve with Youden index. In this way, we found the p-values of $\log_{10}$ HBV DNA (p=0.251), $\log_{10}$ HBsAg (p=0.144), Hb (p=0.104) and pre-treatment NLR (p=0.013) were below 0.3. The optimal cutoffs of these parameters were obtained to transform them into dichotomous variables (optimal cutoffs=7.905 IU/ml, 4.01

Table III. *Regression analysis of the clinical factors associated with post-treatment neutrophil–to–lymphocyte ratio (NLR).*

Characteristic	Regression coefficient	95% CI	*p*-Value
Univariate analysis			
Age, years	−0.020	−0.039–0.000	**0.047**
Gender, male	0.110	−0.538–0.758	0.734
Hepatocellular carcinoma	0.432	−0.774–1.639	0.474
Cirrhosis	0.028	−0.922–0.977	0.953
Ishak histology activity index	−0.009	−0.313–0.295	0.952
Piecemeal necrosis (score>1)	0.168	−0.477–0.812	0.603
Confluent necrosis (score>0)	−0.309	−1.138–0.520	0.457
Focal (spotty) lytic necrosis, apoptosis, and focal inflammation (score>2)	0.169	−0.448–0.786	0.584
Portal inflammation (score>2)	0.029	−0.451–0.510	0.902
Viral serologic analysis			
HBV DNA load, log10 IU/ml	0.027	−0.224–0.278	0.832
HBeAg positive	−0.030	−0.574–0.514	0.911
HBsAg level, $\log_{10}$ IU/ml	−0.121	−0.515–0.274	0.542
Serum biochemistry analysis			
ALT, IU/l	-1.711×10^{-5}	−0.004–0.004	0.993
AST, IU/l	−0.001	−0.008–0.005	0.662
Bilirubin, mg/dl	0.014	−0.644–0.671	0.966
Platelet count, ×1000/mm^3	−0.001	−0.007–0.005	0.738
Hemoglobin, g/dl	−0.106	−0.291–0.080	0.257
Pre-treatment NLR	0.682	0.277–1.087	**0.001**
Pre-treatment PLR	0.000	−0.008–0.007	0.938
Multivariate analysis			
Age, years	0.004	−0.007–0.015	0.473
Pre-treatment NLR	−0.262	−0.445–−0.078	**0.006**

CI, Confidence interval; HBV, hepatitis B virus; HBeAg, hepatitis B virus e antigen; HBsAg, hepatitis B virus surface antigen; ALT, alanine transaminase; AST, aspartate transaminase; GGT; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet–to–lymphocyte ratio. Significant p-values are shown in bold.

Table IV. *Univariate and multivariate analysis of the clinical factors associated with increasing neutrophil–to–lymphocyte ratio (NLR) after peginterferon treatment.*

Characteristic	Odd ratio	95% CI	*p*-Value
Univariate analysis			
Age, years	1.007	0.962-1.054	0.773
Gender, male	0.698	0.185-2.640	0.597
Hepatocellular carcinoma	0.769	0.046-12.807	0.855
Cirrhosis	0.995	0.324-3.058	0.994
Ishak histology activity index	1.042	0.748-1.451	0.809
Piecemeal necrosis (score>1)	2.710	0.666-11.021	0.164
Confluent necrosis (score>0)	0.547	0.113-2.649	0.454
Focal (spotty) lytic necrosis, apoptosis, and focal inflammation (score>2)	1.733	0.525-5.727	0.367
Portal inflammation (score>2)	1.645	0.628-4.307	0.311
Viral serologic analysis			
HBV DNA load, $\log_{10}$	0.803	0.551-1.168	0.251
HBV DNA load, $\log_{10}$ ≥7.905 IU/ml	0.460	0.163-1.295	0.141
HBeAg positive	0.521	0.179-1.513	0.230
HBsAg, $\log_{10}$	0.654	0.370-1.156	0.144
HBsAg, $\log_{10}$ ≥4.01 IU/ml	0.356	0.132-0.956	**0.040**
Serum biochemistry analysis			
ALT, IU/l	1.001	0.997-1.005	0.594
AST, IU/l	1.000	0.994-1.006	0.943
Bilirubin, mg/dl	1.262	0.237-6.731	0.785
Platelet count, ×1,000/mm^3	0.999	0.988-1.009	0.793
Hemoglobin	0.738	0.511-1.064	0.104
Hemoglobin, ≥15.65 g/dl	0.313	0.114-0.853	**0.023**
Pre-treatment NLR	0.320	0.130-0.783	**0.013**
Pre-treatment NLR ≥1.39	0.265	0.098-0.712	**0.008**
Pre-treatment PLR	0.988	0.976-1.001	0.076
Multivariate analysis			
HBsAg, $\log_{10}$ ≥4.01 IU/ml	0.253	0.074-0.863	**0.028**
Hemoglobin, ≥15.65 g/dl	0.170	0.049-0.585	**0.005**
Pre-treatment NLR ≥1.39	0.290	0.096-0.877	**0.028**

CI, Confidence interval; HBV, hepatitis B virus; HBeAg, hepatitis B virus e antigen; HBsAg, hepatitis B virus surface antigen; ALT, alanine transaminase; AST, aspartate transaminase; PLR, platelet–to–lymphocyte ratio. When continuous variables had a *p*-value <0.3, it was assessed as a nominal variable for further analysis according to optimal cut-off point decided by receiver operating characteristic curve with Youden index.

IU/l, 15.65 g/dl, and 1.39, respectively). The obviously opposing trends of ΔNLR were observed in patients portioned by NLR (Figure 1).

As such, it was found that $\log_{10}$ HBs Ag ≥4.01 IU/ml (OR=0.356; 95% CI=0.132-0.956; p=0.040)=Hb ≥15.65 g/dL (OR=0.313; 95% CI 0.114-0.853; p=0.023) and pre-treatment NLR ≥1.39 (OR=0.265; 95% CI=0.098-0.712; p=0.008) were significantly associated with binary NLR change in univariate analysis. In multivariate analysis, it was found that these were all independent factors: $\log_{10}$ HBsAg ≥4.01 IU/ml: OR=0.253, 95% CI=0.074-0.863, adjusted p=0.028; Hb ≥15.65 g/dl: OR=0.170, 95% CI=0.049-0.585, adjusted p=0.028; and pre-treatment NLR ≥1.39: OR=0.290, 95% CI=0.096–0.877, adjusted p=0.028.

A predictive score (PS) was thus formulated: PS=2.095-1.237×pre-treatment NLR_b −1.774×HB_b −1.373×logHBs Ag_b, where NLR_b=1 if NLR ≥1.39, otherwise 0; HB_b=1 if Hb ≥15.65 g/dL, otherwise 0; logHBsAg_b=1 if log HBsAg10 ≥4.01 IU/ml, otherwise 0.

When this score was used to predict ΔNLR, an AUC of 76.5% and optimal cutoff of 0.5 were obtained (OR=101.746; 95% CI=8.701–1189.725; p<0.001) (Figures 2 and 3). The only two HCC cases developed at 20 and 80 months after completing peginterferon treatment, with predictive scores of 0.89 and 0.70, both above the cutoff of 0.5, which predicted an increase of NLR.

Discussion

Several studies had established that a higher NLR was independently associated with early mortality and poor clinical outcomes of HBV-related decompensated liver cirrhosis, resectable and advanced HCC after treatments (radical hepatectomy, radiofrequency ablation, transarterial chemo-

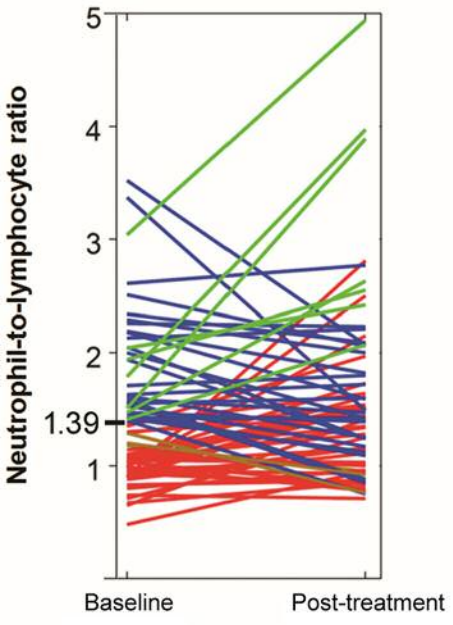

Figure 1. *Negative association between pretreatment neutrophil–to–lymphocyte ratio (NLR) and NLR changes in patients before and after peginterferon treatment. Of 33 patients with pre-treatment NLR ≥1.39, 26 had either no prominent change of NLR (ΔNLR = −0.25 to 0.25) or a substantial decrease (ΔNLR <−0.25) of NLR after peginterferon treatment (blue lines); whereas only seven patients had a substantial increase of NLR (ΔNLR >0.25) (green lines). On the other hand, of 38 patients with NLR <1.39, 35 had either no prominent change of NLR or a substantial increase (ΔNLR >0.25) of NLR (red lines); whereas only three had a substantial decrease of NLR (ΔNLR <−0.25) (brown lines).*

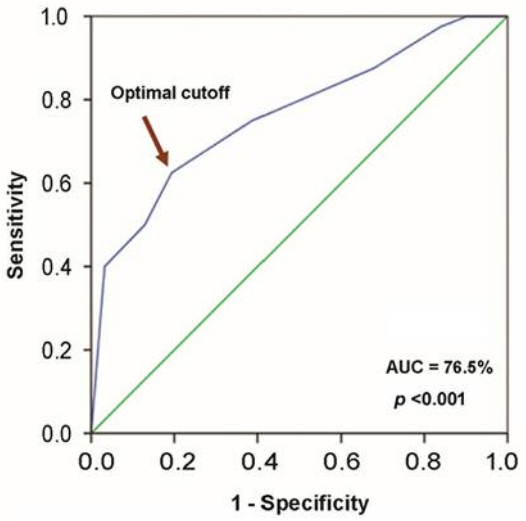

Figure 2. *The performance of the predictive score in prediction of neutrophil-to-lymphocyte ratio (NLR) changes assessed by the receiver operating characteristic curve. The optimum cutoff of the predictive score was 0.5 with sensitivity of 0.625 and specificity of 0.806. AUC: Area under the curve.*

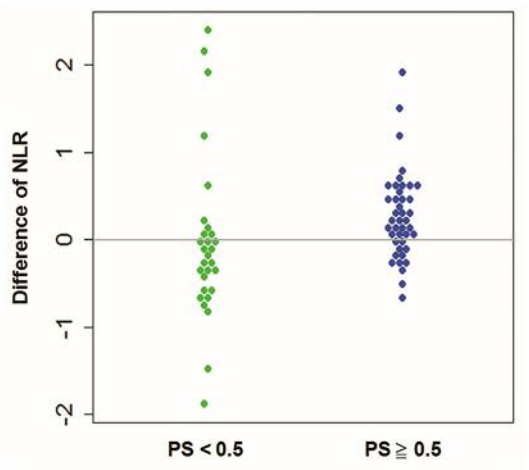

Figure 3. *The scatterplot of difference in neutrophil-to-lymphocyte ratio (NLR) in patients with a predictive score (PS) of <0.5 or ≥0.5.*

embolization, liver transplantation) (31-35). Our recent analysis revealed that peginterferon was superior to nucleos(t)ide in reducing HCC risk (9), and immunomo-dulation may play a significant role. However, the actual immunomodulatory properties linked to the anti-HCC effects were poorly understood. In the present study, a novel and intriguing result was found. The pre-treatment NLR was, in fact, negatively associated with the NLR change before and after peginterferon treatment. Accordingly, patients with chronic hepatitis B with higher pretreatment NLRs were likely to benefit from peginterferon treatment, in terms of HCC prevention.

At this time, the mechanism by which peginterferon negatively regulates NLR is not clear. Conceivably, the NLR is determined by the balance between the rates of neurophils/lymphocytes generation and damage. Myelopoiesis occurrs in bone marrow through multiple steps, which are regulated through several cellular and humoral factors not fully characterized (36). Lymphopoiesis involves even more organs from bone marrow to lymphoid tissues, with several complex developmental steps (37). On the other hand, it is clear that lymphocytes play a major role in HBV-related chronic hepatitis. Infiltration of lymphocytes in the liver lobules was associated with the severity of hepatic inflammation (38). Peginterferon presumably modulated one or more of these processes so that the NLR was changed.

Other factors related to NLR changes included the HBsAg level and Hb level. Again, these were negatively associated with NLR changes. Presumably, higher HBsAg levels are associated with a larger amount of intrahepatic covalently

closed circular DNA (39), and therefore an increase of hepatitis activities is more likely to occur after peginterferon treatment. Under such circumstance, an increased rate of lymphopoiesis could be expected and thus a decreased NLR. On the other hand, anemia is a well-known side-effect of interferon therapy since interferons are potent inhibitors of erythropoiesis (40). Anemia might lead to greater tissue hypoxemia and thus more damage to inflammatory liver tissues and infiltrating lymphocytes. A higher Hb level could provide more oxygen to tissue, resulting in a protective effect. However, the link between less hypoxemia and a decrease in NLR remains to be established.

Finally, we were able to establish a scoring system to predict NLR increase or decrease using these three factors. Interestingly, the two patients who eventually developed HCC both had a score >0.5, which predicted an increase of NLR after peginterferon treatment, and thus an increased risk of HCC. These data imply that the predictive score might be used to select patients who could benefit more (in terms of HCC prevention) when choosing between peginterferon and nucleos(t)ide analogs as anti-HBV therapy.

Conclusion

The pre-treatment NLR, Hb and HBsAg level, in combination, formulated a score which effectively predicts NLR change after peginterferon treatment in patients with chronic hepatitis B. Accordingly, it may be possible to select patients who would benefit most from peginterferon treatment in prevention of HCC.

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