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Pan-Immune-Inflammation Value and Functional Cure in Patients with Chronic Hepatitis B Receiving Long-Term Nucleos(t)ide Analogue Therapy

Uzun Süreli Nükleoz(t)id Analog Tedavisi Alan Kronik Hepatit B Hastalarında Pan-İmmün-Enflamasyon Değeri ve Fonksiyonel Kür

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ABSTRACT

Objectives: Functional cure, defined by hepatitis B surface antigen loss, is the preferred therapeutic endpoint in chronic hepatitis B (CHB). The pan-immune-inflammation value (PIV) is an inflammation-based index derived from routine complete blood count parameters. This study investigated the association between PIV and functional cure in patients with CHB receiving nucleos(t)ide analogue (NA) therapy.

Materials and Methods: This retrospective case-control study included 48 patients who achieved functional cure during NA therapy and 150 patients without functional cure as controls. PIV was evaluated at baseline and month-12. Receiver operating characteristic (ROC) analysis assessed the discriminatory performance of month-12 PIV, and multivariable logistic regression was used to identify factors independently associated with functional cure.

Results: Baseline PIV was comparable between groups, whereas month-12 PIV was significantly lower in the functional cure group (p=0.007). The area under the ROC curve for month-12 PIV was 0.629 [95% confidence interval (CI), 0.535-0.720]. A cut-off value of 148.4 provided 47.9% sensitivity and 73.9% specificity. After adjustment for age, hepatitis B e antigen status, baseline hepatitis B virus-DNA level, and fibrosis score, month-12 PIV≤148.4 remained independently associated with functional cure [adjusted odds ratio (OR), 2.66; 95% CI, 1.29-5.47; p=0.008]. Older age was also independently associated with functional cure (adjusted OR per year, 1.05; 95% CI, 1.02-1.08; p=0.003).

Conclusion: Lower month-12 PIV was independently associated with functional cure during NA therapy. Although its discriminatory ability

ÖZ

Amaç: Fonksiyonel kür, kronik hepatit B (KHB) tedavisinde hepatit B yüzey antijeni kaybı ile tanımlanan tercih edilen tedavi hedefidir. Pan-immün-enflamasyon değeri (PIV), rutin tam kan sayımı parametrelerinden hesaplanan enflamasyon temelli bir indekstir. Bu çalışmada, nükleoz(t)id analoğu (NA) tedavisi alan KHB hastalarında PIV ile fonksiyonel kür arasındaki ilişkinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Bu retrospektif olgu-kontrol çalışmasına, NA tedavisi sırasında fonksiyonel kür gelişen 48 hasta ile fonksiyonel kür gelişmeyen 150 kontrol dahil edildi. PIV başlangıçta ve tedavinin 12. ayında değerlendirildi. On ikinci ay PIV değerinin ayırt edici performansı alıcı işletim karakteristiği (ROC) analizi ile incelendi ve fonksiyonel kür ile bağımsız olarak ilişkili faktörlerin belirlenmesi için çok değişkenli lojistik regresyon analizi yapıldı.

Bulgular: Başlangıç PIV değerleri gruplar arasında benzerken, 12. ay PIV değeri fonksiyonel kür grubunda anlamlı olarak daha düşüktü (p=0,007). On ikinci ay PIV için ROC eğrisi altında kalan alan 0,629 [%95 güven aralığı (GA), 0,535-0,720] idi. 148,4 eşik değeri %47,9 duyarlılık ve %73,9 özgüllük sağladı. Yaş, hepatit B e antijeni durumu, başlangıç hepatit B virüs-DNA düzeyi ve fibrozis skoruna göre düzeltme yapıldıktan sonra, 12. ay PIV≤148,4 fonksiyonel kür ile bağımsız olarak ilişkili bulundu [düzeltilmiş olasılık oranı (OO), 2,66; %95 GA, 1,29-5,47; p=0,008]. İleri yaş da fonksiyonel kür ile bağımsız olarak ilişkiliydi (her bir yıllık yaş artışı için düzeltilmiş OO, 1,05; %95 GA, 1,02-1,08; p=0,003).

Sonuç: Daha düşük 12. ay PIV değeri, NA tedavisi sırasında fonksiyonel kür ile bağımsız olarak ilişkili bulundu. Ayırt edici gücü sınırlı olmakla birlikte

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was modest, PIV may provide a simple and inexpensive marker that could complement clinical and virological factors in the assessment of functional cure.
Keywords: Chronic hepatitis B, functional cure, hepatitis B surface antigen loss, pan-immune-inflammation value, nucleos(t)ide analogue therapy

PIV, fonksiyonel kürün değerlendirilmesinde klinik ve virolojik faktörleri tamamlayabilecek basit ve düşük maliyetli bir belirteç olabilir.
Anahtar Kelimeler: Kronik hepatit B, fonksiyonel kür, hepatit B yüzey antijeni kaybı, pan-immün-enflamasyon değeri, nükleoz(t)id analoğu

Introduction

Despite major advances in antiviral therapy, chronic hepatitis B (CHB) continues to impose a substantial burden through cirrhosis, hepatocellular carcinoma, and liver-related death worldwide (1). Extended treatment with nucleos(t)ide analogs (NAs) effectively suppresses hepatitis B virus (HBV) replication and reduces disease progression. Nevertheless, currently available NAs have little effect on intrahepatic covalently closed circular DNA, making prolonged or lifelong therapy necessary for most patients. Consequently, loss of HBV surface antigen (HBsAg), generally accepted as a functional cure, has become the preferred therapeutic endpoint in CHB (1,2). However, HBsAg clearance remains uncommon during long-term NA therapy, highlighting the need to identify factors associated with functional cure (3,4,5).

Several clinical and virological markers have been evaluated as potential predictors of functional cure. Quantitative HBsAg, HBcrAg, serum HBV-RNA, HBV-DNA, and HBeAg status are among the most extensively studied biomarkers (6). However, several of these assays are not routinely available, limiting their widespread applicability. Long-term NA therapy may also modulate host immune responses, supporting interest in accessible biomarkers of immune-inflammatory changes during treatment (3,7). Inflammation-based indices derived from routine hematological parameters have therefore gained interest as inexpensive biomarkers in CHB (8). The pan-immune-inflammation value (PIV), derived from neutrophil, monocyte, platelet, and lymphocyte counts, was initially developed as a prognostic biomarker in oncology and has subsequently been evaluated in chronic liver disease (9,10). Although several hemogram-derived inflammatory indices have been investigated in CHB, evidence regarding the association between PIV and functional cure remains limited. Therefore, we investigated the association of baseline and month-12 PIV with functional cure in patients with CHB receiving NA therapy.

Materials and Methods

Study Design

This retrospective case-control study included adults with chronic HBV infection receiving nucleos(t)ide analogue (NA) therapy. Patients who achieved functional cure during follow-up constituted the case group, whereas patients who did not achieve functional cure constituted the control group. Patients with human immunodeficiency virus, hepatitis C virus, or hepatitis D virus coinfection, acute infections unrelated to HBV, hematological disorders, malignancy, autoimmune disease, pregnancy, immunosuppressive therapy, or missing clinical or laboratory data were excluded.

Demographic characteristics, antiviral treatment, treatment and follow-up durations, biochemical and virological parameters, complete blood count results, and histological findings were extracted from the hospital electronic database. Laboratory parameters included alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total bilirubin, platelet count, white blood cell count, neutrophil count, lymphocyte count, and monocyte count. Virological parameters included HBeAg status, serum HBV-DNA, and HBsAg status. Histological activity index (HAI) and fibrosis scores were recorded when available. AST to platelet ratio index (APRI) and fibrosis-4 index (FIB-4) were calculated from the relevant laboratory and clinical parameters. Serum HBsAg was assessed annually as part of routine follow-up.

Functional cure was defined as sustained HBsAg loss during antiviral therapy, continuation of NA treatment for at least 12 months after HBsAg loss, subsequent treatment discontinuation, persistent HBsAg negativity for at least 24 weeks after treatment withdrawal, and undetectable serum HBV-DNA throughout post-treatment follow-up. Anti-HBs seroconversion was not required.

PIV was the primary study variable and was evaluated at baseline and month 12, when laboratory data were available for all participants. In patients who achieved functional cure, laboratory results from the visit documenting HBsAg loss and the final post-treatment follow-up were also reviewed to confirm the outcome.

The study protocol was approved by the Sakarya University Health Sciences Scientific Research Ethics Committee (approval no: E-43012747-050.04-596826-561, date: 17.06.2026). The requirement for informed consent was waived because of the retrospective design of the study.

Laboratory Assessment

Complete blood count parameters were measured using an automated hematology analyzer. PIV was calculated as follows:

PIV = neutrophil count × monocyte count × platelet count / lymphocyte count

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Normality was assessed using the Kolmogorov-Smirnov test. Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables as counts and percentages.

Continuous variables were compared using the independent-samples t-test or Mann-Whitney U test, and categorical variables using the chi-square test or Fisher's exact test, as appropriate.

The discriminatory performance of baseline and month-12 PIV for functional cure was assessed using receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC), with the optimal cutoff determined by the Youden index.

Logistic regression was used to identify factors independently associated with functional cure. Variables included in the adjusted analysis were selected a priori based on clinical importance, prior evidence, and the number of outcome events to minimize model overfitting. Because neutrophil, monocyte, lymphocyte, and platelet counts are mathematical components of the PIV equation, these variables were excluded from the multivariable analysis to avoid multicollinearity. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. Statistical significance was defined as a two-sided p-value <0.05.

Results

Baseline Characteristics

The study included 48 patients who achieved functional cure during NA therapy and 150 patients without functional cure who constituted the control group. Baseline demographic, clinical, and laboratory characteristics of the two groups are presented in Table 1.

Patients in the functional cure group were significantly older than those in the non-functional cure group (56.4±11.9 vs. 49.4±12.1 years, p<0.001). The baseline fibrosis score was also significantly higher in the functional cure group (p<0.001). Neutrophil counts were significantly lower in the functional cure group (p<0.001), as were lymphocyte counts (p=0.030). No significant differences were observed between the groups in sex, HBeAg positivity, baseline HBV-DNA level, HAI score, treatment or follow-up duration, ALT, AST, albumin, platelet count, monocyte count, or baseline PIV.

Laboratory Findings at Month 12

The laboratory findings at month 12 are summarized in Table 2. Compared with the non-functional cure group, patients in the functional cure group had significantly lower AST levels, white blood cell counts, neutrophil counts, lymphocyte counts, platelet counts, serum albumin levels, and PIV values. Total bilirubin levels were significantly higher in the functional cure group. No significant differences were observed in ALT, monocyte count, APRI, or FIB-4. Among the inflammatory indices evaluated, month-12 PIV was significantly lower in the functional cure group [167.80 (97.89-239.80) vs. 209.37 (146.88-304.36), p=0.007].

Receiver Operating Characteristic Analysis

ROC curve analysis was performed to evaluate the ability of month-12 PIV to discriminate between patients with and without functional cure. The AUC was 0.629 (95% CI, 0.535-0.720). The optimal cut-off value determined using the Youden index was 148.4, with a sensitivity of 47.9% and a specificity of 73.9% (Figure 1).

Logistic Regression Analysis

Variables with established clinical relevance were included in the multivariable logistic regression model (Table 3). In the univariable analysis, increasing age, higher fibrosis score, and low month-12 PIV (≤148.4) were significantly associated with functional cure. After adjustment for age, HBeAg status, baseline HBV-DNA level, and fibrosis score, low month-12 PIV remained independently associated with functional cure (adjusted OR, 2.66; 95% CI, 1.29-5.47; p=0.008).

Table 1. Baseline demographic, clinical, and laboratory characteristics according to functional cure status

Variable	Functional cure group (n=48)	Non-functional cure group (n=150)	p-value
Age (years)	56.4±11.9	49.4±12.1	<0.001
Male sex, n (%)	28 (58.3)	95 (63.3)	0.609
HBeAg positivity, n (%)	8 (16.7)	22 (15.2)	0.820
Baseline HBV-DNA (IU/mL)	12,490.5 (2,995.8-463,791.8)	40,206.5 (3,502.5-3,533,199.8)	0.36
HAI score	6 (6-9)	7 (6-8.8)	0.985
Fibrosis score	2 (2-3)	2 (1-2.75)	<0.001
Treatment duration (months)	96 (72-126)	92 (68-121)	0.48
Follow-up duration (months)	118 (90-144)	114 (88-140)	0.57
ALT (U/L)	30.5 (19.0-68.3)	37.5 (20.0-69.5)	0.958
AST (U/L)	25.5 (19.0-55.0)	31.0 (22.0-48.8)	0.545
Albumin (g/dL)	4.2 (3.95-4.40)	4.2 (4.0-4.4)	0.737
Platelet count (×10^3/μL)	197 (146.8-259.3)	220.5 (183.8-258.5)	0.062
Neutrophil count (×10^3/μL)	3.55 (2.40-4.03)	4.04 (3.26-5.18)	<0.001
Lymphocyte count (×10^3/μL)	1.91±0.71	2.17±0.74	0.03
Monocyte count (×10^3/μL)	0.50 (0.36-0.60)	0.47 (0.38-0.60)	0.961
Pan-immune-inflammation value	185.7 (91.2-254.7)	201.3 (134.3-279.3)	0.083

Data are presented as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, and n (%) for categorical variables, as appropriate. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HAI: Histological activity index, HBeAg: Hepatitis B e antigen, HBV: Hepatitis B virus

Table 2. Laboratory findings at month 12 according to functional cure status

Variable	Functional cure group (n=48)	Non-functional cure group (n=150)	p-value
ALT (U/L)	20.50 (15.00-32.50)	21.00 (16.00-32.00)	0.757
AST (U/L)	22.00 (18.00-27.00)	25.00 (20.00-32.00)	0.014
Total bilirubin (mg/dL)	0.70 (0.52-0.99)	0.60 (0.44-0.77)	0.011
Albumin (g/dL)	4.20 (3.90-4.40)	4.40 (4.10-4.50)	0.013
White blood cell count (×10³/μL)	5.88 (4.88-7.97)	6.84 (5.69-8.21)	0.021
Neutrophil count (×10³/μL)	3.51 (2.51-4.46)	4.11 (3.20-4.96)	0.010
Lymphocyte count (×10³/μL)	1.88±0.68	2.20±0.76	0.010
Monocyte count (×10³/μL)	0.45 (0.33-0.56)	0.44 (0.38-0.56)	0.838
Platelet count (×10³/μL)	197.40±59.10	251.22±67.63	<0.001
APRI	0.21 (0.18-0.32)	0.20 (0.16-0.27)	0.154
FIB-4	0.16 (0.08-0.26)	0.10 (0.07-0.19)	0.118
PIV	167.80 (97.89-239.80)	209.37 (146.88-304.36)	0.007

Data are presented as mean ± standard deviation for normally distributed continuous variables and median (interquartile range) for non-normally distributed continuous variables, as appropriate. PIV: Pan-immune-inflammation value, APRI: Aspartate aminotransferase-to-platelet ratio index, FIB-4: Fibrosis-4 index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Table 3. Univariable and multivariable logistic regression analyses for factors associated with functional cure

Variable	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
Age, per 1-year increase	1.048 (1.019-1.077)	<0.001	1.047 (1.015-1.079)	0.003
Sex, female vs male	1.234 (0.636-2.394)	0.535	—	—
HBeAg positivity	1.118 (0.462-2.708)	0.804	1.559 (0.576-4.222)	0.382
Baseline HBV-DNA, per 1-log10 IU/mL increase	0.888 (0.735-1.074)	0.221	0.926 (0.749-1.145)	0.479
Fibrosis score, per 1-point increase	1.517 (1.106-2.081)	0.010	1.316 (0.923-1.875)	0.129
Low month-12 PIV (≤148.4)	2.611 (1.324-5.149)	0.006	2.659 (1.292-5.469)	0.008

OR: Odds ratio, CI: Confidence interval, PIV: Pan-immune-inflammation value, HBV: Hepatitis B virus, HBeAg: Hepatitis B e antigen

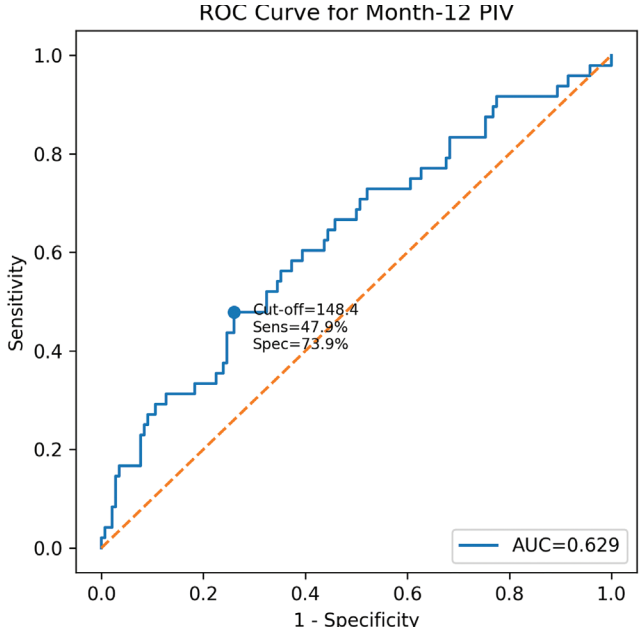

Figure 1. Receiver operating characteristic (ROC) curve for month-12 pan-immune-inflammation value (PIV) in discriminating patients with and without functional cure

AUC: Area under the curve

Increasing age was also independently associated with functional cure (adjusted OR, 1.05 per year; 95% CI, 1.02-1.08; p=0.003). HBeAg status, baseline HBV-DNA level, and fibrosis score were not independently associated with functional cure.

Discussion

Functional cure has emerged as the preferred therapeutic goal in CHB because of its well-established association with improved long-term clinical outcomes. Nevertheless, despite persistent inhibition of HBV replication during NA therapy, HBsAg loss remains an infrequent event (3). As a result, considerable attention has been directed toward identifying factors that may predict functional cure. Most previous studies have focused on virological biomarkers, particularly quantitative HBsAg, HBcrAg, and serum HBV-RNA (11,12). Although these biomarkers have demonstrated prognostic value, their incorporation into routine clinical practice remains limited because the required assays are not universally available.

PIV was initially introduced as a composite index based on neutrophil, monocyte, platelet, and lymphocyte counts (9). By integrating several circulating cell populations rather than relying on a single-cell count or a two-cell ratio, PIV may provide a broader representation of systemic immune-inflammatory status.

Its clinical relevance has subsequently been explored in cancer, metabolic disorders, and chronic liver diseases (13). Because chronic HBV infection is characterized by persistent immune dysregulation involving both innate and adaptive immune responses, a composite index incorporating multiple peripheral immune-cell populations may offer a more informative view of the immune milieu than indices derived from fewer cell types (14).

Patients who achieved functional cure during long-term NA therapy exhibited significantly lower month-12 PIV values than those who did not achieve functional cure. This association persisted after adjustment for age, HBeAg status, baseline HBV-DNA level, and fibrosis score, indicating that month-12 PIV was independently associated with functional cure. Given that PIV is calculated from routinely available complete blood count parameters, it may serve as a simple, inexpensive indicator of the peripheral immune-inflammatory milieu associated with functional cure during antiviral treatment.

ROC analysis showed that month-12 PIV had modest discriminatory ability for functional cure, with an AUC of 0.629. The identified cut-off value of 148.4 had a specificity of 73.9% but a relatively low sensitivity of 47.9%. These findings suggest that PIV alone is unlikely to be sufficient as a predictive marker for functional cure, but it may have value as part of a broader assessment together with virological and clinical factors.

Several complementary biological mechanisms likely explain the association between lower PIV values and functional cure. Current evidence indicates that functional cure reflects not only durable suppression of HBV replication but also progressive recovery of antiviral immune function during prolonged NA therapy (3,15). Although complete restoration of HBV-specific immunity is rarely achieved, sustained viral suppression has been shown to partially reverse T-cell dysfunction and alleviate the chronic immune dysregulation characteristic of persistent HBV infection (8,14). Growing evidence indicates that long-term antiviral therapy is accompanied by dynamic remodeling of both innate and adaptive immune-cell compartments, a process that parallels improved virological control and the eventual achievement of functional cure (16,17). These observations provide a biological basis for evaluating composite blood-cell indices such as PIV as indirect indicators of the evolving immune-inflammatory environment, while recognizing that they do not directly quantify HBV-specific immune responses.

The biological significance of PIV in chronic HBV infection can be better appreciated by considering the immunological functions of its cellular components. Neutrophils are an essential part of the innate immune response; however, chronic HBV infection has been shown to compromise their antimicrobial activity by suppressing neutrophil extracellular trap formation through alterations in reactive oxygen species generation and autophagy (18,19). Monocytes serve as an important interface between innate and adaptive immunity by contributing to antigen presentation and cytokine production. Exposure to HBV antigens may promote both inflammatory cytokine release and the development of immunoregulatory monocyte phenotypes that attenuate responses mediated by HBV-specific T-cells, B cells, and natural killer cells (16,20). Beyond their established function in hemostasis, platelets actively modulate hepatic immune responses by facilitating the recruitment of virus-specific $CD8^+$ T-cells and other inflammatory leukocytes to the liver (21,22). At the same time, circulating platelet counts may also reflect the presence of hepatic fibrosis, cirrhosis, and the overall severity of chronic liver disease (23). In our study, neutrophil and platelet counts were significantly lower in the functional cure group at month 12, whereas monocyte counts did not differ between groups. Lymphocyte counts were also lower despite forming the denominator of the PIV equation. These findings suggest that the lower PIV observed in the functional cure group reflects the combined behavior of its cellular components rather than a uniform change in any single cell population. The lower lymphocyte count observed in the functional cure group should be interpreted cautiously. Peripheral lymphocyte counts provide only a broad measure of the adaptive immune compartment and do not directly reflect HBV-specific immune activity. Functional cure is thought to depend primarily on effective HBV-specific $CD8^+$ cytotoxic T-cell activity, while $CD4^+$ T-cells provide the helper signals required for the generation, maintenance, and coordination of antiviral immunity (14,24). Therefore, a lower total peripheral lymphocyte count should not necessarily be interpreted as evidence of a weaker HBV-specific immune response.

The rationale for PIV is to integrate neutrophils, monocytes, and platelets in the numerator with lymphocytes in the denominator, providing an integrated, although non-specific, measure of the interplay between peripheral innate inflammatory activity and adaptive immune function. Although this measure does not directly assess HBV-specific antiviral immunity, the lower month-12 PIV observed in patients who subsequently achieved functional cure is biologically consistent with a more favorable immune-inflammatory environment during prolonged antiviral therapy. This concept is further supported by recent single-cell studies demonstrating coordinated remodeling of innate and adaptive immune cell populations in individuals who achieve a functional cure (17). To our knowledge, evidence linking PIV to functional cure in patients undergoing long-term NA therapy for CHB has not been reported previously.

Fibrosis scores were statistically different between the groups; however, this finding should be interpreted cautiously. Although the median fibrosis score was 2 in both groups, the distribution of fibrosis stages differed, with fibrosis scores in the functional cure group predominantly clustered at F2-F3. Moreover, controls were not individually matched to cases according to fibrosis stage. Thus, the observed difference may partly reflect differences in the distribution of fibrosis stages and the case-control sampling structure rather than a direct association between fibrosis severity and functional cure. For this reason, fibrosis score was included as an adjustment variable in the multivariable analysis.

Study Limitations

Several limitations should be considered when interpreting these findings. Because this was a retrospective study conducted at a single tertiary referral center, the applicability of the results to other populations may be limited. In addition, the observational design precludes any conclusions regarding causality. Although the multivariable analyses accounted for major clinical confounders, residual confounding cannot be entirely excluded. In addition, because PIV is calculated from routine peripheral blood cell counts, it provides only an indirect estimate of the peripheral immune-inflammatory milieu rather than HBV-specific immune function. Consequently, HBV-specific $CD4^+$ and $CD8^+$ T-cell responses, immune-cell phenotypes, cytokine profiles, and other immunological markers that might further explain the observed association were not available for analysis. Moreover, the present study evaluated PIV only at month 12, and longitudinal changes throughout antiviral treatment were not investigated. Nevertheless, the relatively large number of patients who achieved functional cure, along with adjustment for major clinically relevant confounders, enhances the robustness of our findings.

Conclusion

Lower month-12 PIV was independently associated with functional cure among patients with CHB managed with long-term NA therapy. This study identified an independent association between PIV and HBsAg loss in this clinical setting. As PIV is derived from routinely available complete blood count parameters at no additional cost, it may serve as a practical biomarker associated with functional cure. However, PIV should be interpreted as an indirect indicator of the peripheral immune-inflammatory milieu rather than a direct measure of HBV-specific immune restoration. Further prospective multicenter studies incorporating serial PIV measurements and detailed immunological profiling are warranted to confirm these findings and better define the role of PIV in patients receiving NA therapy.

Ethics

Ethics Committee Approval: The study protocol was approved by the Sakarya University Health Sciences Scientific Research Ethics Committee (approval no: E-43012747-050.04-596826-561, date: 17.06.2026).

Informed Consent: The requirement for informed consent was waived because of the retrospective design of the study.

Footnotes

Financial Disclosure: The author declares no financial support.

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