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Original Article

HBeAg clearance in chronic Hepatitis B: is it predictable?

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Abstract

Introduction: Prediction of HBeAg loss is crucial for understanding the prognosis of chronic hepatitis B (CHB) and determining when to discontinue treatment. We aimed to identify factors predicting HBeAg clearance in patients undergoing antiviral treatment for HBeAg-positive CHB

Methodology: This retrospective study included patients who started antiviral treatment for HBeAg-positive CHB from January 1, 2008, to December 31, 2022, with at least one year of follow-up. We evaluated age, platelet count, treatment duration, ALT × Upper limit of normal (ULN), AST × ULN, AST/ALT ratio, Albumin-Bilirubin grade (ALBI), Platelet-Albumin-Bilirubin grade (PALBI), AST-Platelet ratio index (APRI), and Fibrosis-4 (FIB-4) parameters. ROC analysis was used to assess these parameters' ability to predict HBeAg loss.

Results: Ninety-four patients were included, 43 (45.7%) of whom were female. HBeAg clearance occurred in 32 (34%) patients. Treatment duration was significantly longer in patients with HBeAg clearance ($p = 0.003$). Patients with HBeAg clearance had significantly higher median age, fibrosis score (FS), APRI, and FIB-4 values ($p = 0.028$, $p = 0.024$, $p = 0.008$, and $p = 0.003$, respectively) and lower mean platelet count ($p = 0.010$) at treatment initiation. ROC analysis identified age, FS, APRI, FIB-4, and platelet count as significant predictors, with APRI having the highest area under the curve (AUC = 0.771, $p = 0.007$, sensitivity 65%, specificity 66.7% for the cut-off value of 0.71).

Conclusions: This study highlights the potential of FIB-4, platelet count, and particularly APRI in predicting HBeAg clearance. These findings can aid clinicians in optimizing treatment strategies and improving patient outcomes.

Key words: Antiviral; APRI; FIB-4; HBeAg clearance.

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Introduction

Chronic hepatitis B (CHB) remains a major global health concern, affecting an estimated 254 million people worldwide in the year 2022 and causing over one million new infections each year [1]. The persistent nature of CHB is particularly concerning due to its association with severe liver-related complications, including cirrhosis, hepatocellular carcinoma, and even death. Antiviral therapy has been identified as a crucial intervention to prevent these complications, effectively reducing viral load, halting disease progression, and improving survival outcomes [2,3]. However, these benefits often come with the necessity for prolonged or even lifelong treatment, raising the question of when, if ever, it is appropriate to discontinue therapy.

Deciding when to discontinue antiviral therapy in CHB patients is a critical aspect of clinical management that requires careful consideration. This decision should be made cautiously to preserve positive patient outcomes. Specific endpoints for discontinuing treatment were identified. The ideal endpoint is the loss of HBsAg. The observation of biochemical response or the development of hepatitis B e antigen (HBeAg) loss in HBeAg-positive patients are also achievable endpoints [4-5]. HBeAg clearance, whether spontaneous or treatment-induced, has been shown to significantly reduce the risk of cirrhosis and hepatocellular carcinoma, and improve overall survival, making it a key milestone in the management of HBeAg-positive CHB patients [6].

Given the clinical importance of treatment endpoints, accurate prediction of HBeAg loss also plays an important role in predicting disease prognosis and optimal treatment discontinuation goals. In this study, we aimed to evaluate factors that may predict HBeAg clearance in patients receiving antiviral treatment due to HBeAg-positive CHB.

Methodology

This retrospective descriptive study included

Table 1. Formulas of the parameters to be evaluated in the study.

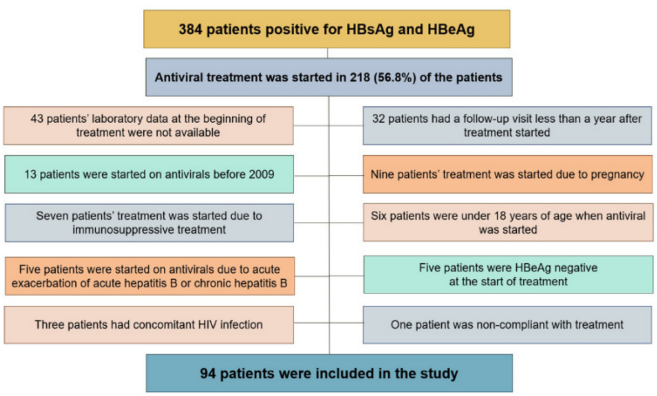
Parameters	Formulas
ALT x ULN	ALT (U/L) / ULN
AST x ULN	AST (U/L) / ULN
AST/ALT ratio	AST / ALT
ALBI	($\log_{10}$ bilirubin (umol/L) × 0.66) + (albumin (g/L) × -0.085)
PALBI	2.02 × $\log_{10}$ bilirubin (umol/L) − 0.37 × ($\log_{10}$ bilirubin (umol/L))^2 − 0.04 × albumin (g/L) − 3.48 × $\log_{10}$ platelet (10^3/uL) + 1.01 × ($\log_{10}$ platelet (10^3/uL))^2
APRI	((AST (U/L) / ULN) / Platelet (10^9/L) × 100
FIB-4	(Age (years) × AST (U/L)) / (platelet (10^9/L) × √ (ALT (U/L))

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ULN: Upper limits of normal; ALBI: Albumin-Bilirubin grade; PALBI: Platelet-Albumin-Bilirubin grade; APRI: Aspartate aminotransferase – Platelet ratio index; FIB-4: Fibrosis-4 index.

patients with HBeAg-positive CHB who initiated antiviral treatment between January 1, 2008, and December 31, 2022. All patients were treated and followed at our hospital for a minimum of one year. Exclusion criteria involved patients under 18 years at the beginning of treatment, incomplete laboratory data, co-infections with other viral hepatitis or HIV, initiation of treatment due to acute hepatitis B, CHB acute exacerbation, pregnancy, or the initiation of immunosuppressive therapy, poor treatment adherence, and those with less than one year of follow-up. We collected data on patient demographics, liver histopathology results, laboratory values (including hepatic transaminases, bilirubin, albumin levels, platelet (PLT) count, HBV DNA level, HBsAg, anti-HBs, HBeAg, and anti-HBe) at the beginning of the treatment, the total duration of treatment, whether HBeAg loss was observed during follow-up, and date of the development of HBeAg loss were retrospectively collected via the hospital information operating system. HBeAg clearance was defined as the loss of HBeAg in an HBeAg-positive CHB patient, regardless of whether anti-HBe was observed.

To predict HBeAg clearance, several parameters were assessed, including alanine aminotransferase (ALT) × upper limit of normal (ULN), aspartate aminotransferase (AST) × ULN, AST/ALT ratio, Albumin-Bilirubin grade (ALBI), Platelet-Albumin-Bilirubin grade (PALBI), AST-Platelet ratio index (APRI) and Fibrosis-4 (FIB-4). The formulas for these parameters are presented in Table 1. The ULN value was accepted as 40 U/L for ALT according to the APASL guideline and 34 U/L for AST, according to laboratory reference ranges [7].

Figure 1. Patient selection and inclusion criteria for the study.



Statistical analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) Version 22.0 (Armonk, NY: IBM Corp) program. The normal distribution of variables was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive analyses were presented as mean (± standard deviation) for normally distributed data and median (minimum-maximum) for non-normally distributed data. Difference between groups in the cross-tables was compared using the Chi-square, and Fisher tests in cases where the values observed in the cells did not meet the Chi-square test assumptions Normally distributed data were evaluated using the independent sample *t*-test, while non-normally distributed data were assessed using the Mann-Whitney U test. Receiver operating characteristic (ROC) curve analysis was employed to evaluate the predictive ability of identified parameters for HBeAg loss. Significant cut-off values were established, and the sensitivity and specificity values were presented. The power of the study was calculated using G*Power 3.1.9.2, which yielded 87.8% with an effect size of 0.8 and a margin of error of 0.05. A p of < 0.05 was considered statistically significant.

Ethics

Ethics committee approval was obtained from our hospital on June 13, 2024, under decision number 2024/130. The study adhered to the principles outlined in the Helsinki Declaration. Due to the retrospective design of the study, informed consent from patients was not required and was not obtained.

Results

Ninety-four patients met the inclusion criteria for this study (Figure 1). Among these patients, 43 (45.7%) were female, and the median age at the treatment initiation was 35 years (range: 18 - 79 years). Liver biopsy results were available for 66 patients, with a median HAI score of 8 (range: 2-16) and a median fibrosis score of 2 (range: 1-6). The baseline laboratory values, liver histopathology results, and other evaluated parameters are presented in Table 2. HBeAg clearance was observed in 32 patients (34%) during treatment. The mean duration of treatment required to achieve HBeAg clearance was 50.3 ± 32.1 months. The overall treatment duration was statistically significantly longer in patients who achieved HBeAg clearance compared to those who did not ($p = 0.003$).

Patients who experienced HBeAg clearance had statistically significantly higher median age, fibrosis score (FS), APRI, and FIB-4 values ($p = 0.028$, $p = 0.024$, $p = 0.008$, and $p = 0.003$, respectively), as well as lower mean PLT count ($p = 0.010$) at treatment initiation compared to those who did not achieve HBeAg clearance. No statistically significant associations were found between HBeAg clearance and other evaluated parameters (Table 3).

In the ROC analysis; the predictive values of age, FS, APRI, FIB-4, and PLT were assessed. Among these, APRI demonstrated the highest area under the curve (AUC) (AUC = 0.771, $p = 0.007$), indicating its

Table 2. Demographic characteristics of the patients and parameters determined at the beginning of the first antiviral treatment.

Parameters	Value
Sex (n = 94) [n (%)]	
Female	43 (45.7)
Male	51 (54.3)
Age (years) (n = 94) [median (min-max)]	35 (18 – 79)
Total duration of antiviral treatment (months) (n = 94) [median (min-max)]	64 (16 – 170)
Liver histopathology results (n = 66) [median (min-max)]	
Histologic activity index	8 (2 – 16)
Fibrosis score	2 (1 – 6)
Laboratory results	
ALT (U/L) (n = 94) [median (min-max)]	64 (10 – 785)
AST (U/L) (n = 94) [median (min-max)]	41 (15 – 330)
Total bilirubin (mg/dL) (n = 75) [median (min-max)]	0.7 (0.2 – 2.4)
Albumin (n = 67) (g/dL) [median (min-max)]	4.2 (3.1 – 5.1)
Platelet (10^3/uL) (n = 93) (mean ± standard deviation)	218 ± 65.9
HBV-DNA ($\log_{10}$ IU/mL) (n = 62) [median (min-max)]	8.1 (2.4 – 11.2)
Serological results	
HBeAg clearance (n = 94) [n (%)]	32 (34)
Time from first treatment initiation to HBeAg clearance (months) (n = 32) (mean ± standard deviation)	50.3 ± 32.1
Scores	
ALT (x ULN) (n = 94) [median (min-max)]	1.60 (0.25 – 19.63)
AST (x ULN) (n = 94) [median (min-max)]	1.21 (0.44 – 9.71)
AST/ALT ratio (n = 94) [median (min-max)]	0.65 (0.29 – 2)
APRI (n = 93) [median (min-max)]	0.60 (.20 – 4.06)
ALBI (n = 65) [median (min-max)]	-2.79 (-3.59 – -1.66)
PALBI (n = 65) (mean ± standard deviation)	-2.48 ± 0.31
FIB-4 (n = 93) [median (min-max)]	0.79 (0.27 – 8.42)

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ULN: Upper limits of normal; ALBI: Albumin-Bilirubin grade; PALBI: Platelet-Albumin-Bilirubin grade; APRI: Aspartate aminotransferase – Platelet ratio index; FIB-4: Fibrosis-4 index.

Table 3. Distribution of patients' demographic characteristics and evaluated parameters according to HBeAg clearance status under antiviral treatment.

Parameters	HBeAg Clearance		*p* value
	No	Yes	
Sex (n = 94) [n (%)]			
Female	33 (64.7)	18 (35.3)	0.952*
Male	29 (67.4)	14 (32.6)	
Age (years) (n = 94) [median (min-max)]	32.5 (18 – 79)	39.5 (18 – 74)	0.028†
Total duration of antiviral treatment (months) (n = 94) [median (min-max)]	56 (16 – 170)	82.5 (16 – 156)	0.003†
Liver histopathology results (n = 66) [median (min-max)]			
Histologic activity index	7 (2 – 16)	9 (3 – 15)	0.279†
Fibrosis score	2 (1 – 6)	3 (2 – 5)	0.024†
Laboratory results			
ALT (U/L) (n = 94) [median (min-max)]	56.5 (14 – 785)	74 (10 – 669)	0.180†
AST (U/L) (n = 94) [median (min-max)]	38.5 (15 – 330)	49 (20 – 302)	0.051†
Total bilirubin (mg/dL) (n = 75) [median (min-max)]	0.7 (0.3 – 2.4)	0.8 (0.2 – 2.4)	0.387†
Albumin (n = 67) (g/dL) [median (min-max)]	4.2 (3.1 – 4.8)	4.1 (3.3 – 5.1)	0.429‡
Platelet (10^3/uL) (n = 93) (mean ± standard deviation)	230.3 ± 61.7	193.3 ± 12.2	0.010‡
HBV-DNA ($\log_{10}$ IU/mL) (n = 62) [median (min-max)]	8.3 (3.8 – 11.2)	7.7 (2.4 – 9.5)	0.251†
Scores			
ALT (x ULN) (n = 94) [median (min-max)]	1.41 (0.35 – 19.63)	1.85 (0.25 – 16.73)	0.180†
AST (x ULN) (n = 94) [median (min-max)]	1.13 (0.44 – 9.71)	1.44 (0.59 – 8.88)	0.051†
AST/ALT ratio (n = 94) [median (min-max)]	0.65 (0.29 – 1.8)	0.64 (0.32 – 2.0)	0.681†
APRI (n = 93) [median (min-max)]	0.51 (0.20 – 3.96)	0.74 (0.25 – 4.06)	0.008†
ALBI* (n = 65) [median (min-max)]	-2.82 (-3.36 – -1.66)	-2.73 (-3.59 – -1.77)	0.172†
PALBI (n = 65) (mean ± standard deviation)	-2.48 ± 0.28	-2.48 ± 0.37	0.978‡
FIB-4 (n = 93) [median (min-max)]	0.72 (0.27 – 8.42)	1.29 (0.38 – 7.33)	0.003†

*Chi-square test was used. † Mann-Whitney U test was used. ‡ Independent sample t-test was used. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ULN: Upper limits of normal; ALBI: Albumin-Bilirubin grade; PALBI: Platelet-Albumin-Bilirubin grade; APRI: Aspartate aminotransferase – Platelet ratio index; FIB-4: Fibrosis-4 index.

superior predictive capability. For a cut-off value of 0.71, APRI exhibited 65% sensitivity and 66.7% specificity (Figure 2).

Discussion

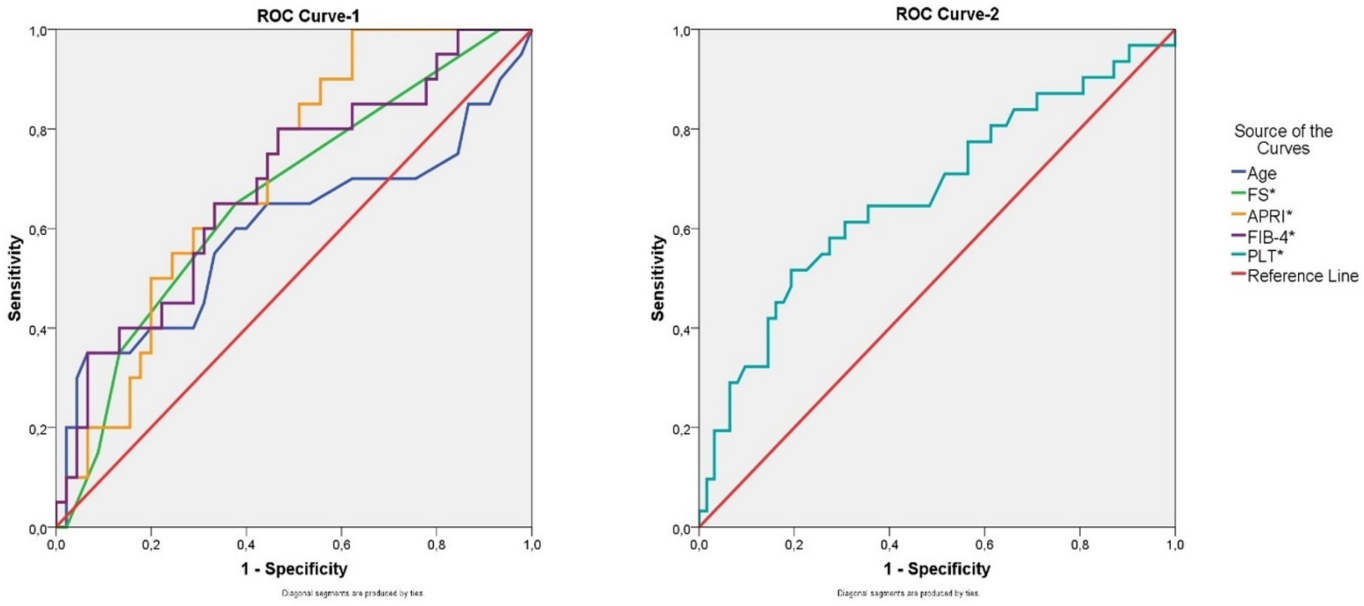
The findings of our study provide valuable insights into the potential predictors of HBeAg in patients with HBeAg-positive CHB undergoing antiviral treatment. The results indicate that parameters such as PLT count, FIB-4, FS, and especially APRI, can serve as significant markers for predicting HBeAg loss.

This study revealed that 34% of patients achieved HBeAg clearance during treatment. The total treatment duration for those who achieved HBeAg clearance was statistically significantly longer compared to those who did not achieve it. Similar to our study, the literature reports HBeAg clearance rates between 25-42% under antiviral treatment [8-10]. In addition, the likelihood of HBeAg seroconversion increases with longer follow-up periods, suggesting that prolonged antiviral therapy may be necessary to achieve HBeAg clearance in CHB patients [10-12].

The key finding of our study was the significant association between HBeAg clearance and several factors such as age, FS, APRI, FIB-4, and PLT count at the initiation of treatment. Patients who achieved HBeAg clearance had higher median age, FS, APRI, and FIB-4 values, as well as lower mean PLT counts compared to those who did not achieve. Among these factors, APRI stood out as a particularly strong predictor of HBeAg clearance, as indicated by its performance with having the highest AUC in the ROC analysis. These findings highlight the potential role of these factors in predicting HBeAg clearance in patients undergoing antiviral treatment.

Several studies have correlated older age with higher rates of HBeAg loss in CHB patients. Chu *et al.* [13] found that age over 30 years independently associated with higher rates of HBeAg seroconversion. Similarly, Buster *et al.* [14] reported an increased

Figure 2. Results of the ROC analysis to evaluate HBeAg clearance. Larger test results in ROC Curve-1 and smaller test results in ROC Curve-2 are indicative of increased HBeAg clearance.



	AUC (95% CI)*	p	Cut-off	Sensitivity (%)	Specifity (%)
Age	.596 (.427 - .764)	.222			
FS*	.663 (.521 - .806)	.037	2.5	65.0	62.2
APRI*	.771 (.586 - .836)	.007	.71	65.0	66.7
FIB-4*	.687 (.546 - .827)	.017	1.01	65.0	66.7
PLT*	.669 (.548 - .791)	.008	207	64.5	64.5

*FS: Fibrosis score; APRI: Aspartate aminotransferase – Platelet ratio index; FIB-4: Fibrosis-4 index; PLT: Platelet; AUC: Area under the ROC curve; CI: Confidence interval.

likelihood of HBeAg loss with advancing age. In another study, although no relationship was found between older age and HBeAg clearance, a significant relationship was reported between HBsAg clearance. In another study, while no association was found between older age and HBeAg clearance, a significant relationship was reported with HBsAg clearance [15]. It could be assumed that older individuals have been infected with the hepatitis B virus for a longer duration. This might increase the likelihood of clearance, which could explain why patients with HBeAg clearance in our study were older.

A noteworthy aspect of this study is the role of fibrosis in HBeAg clearance. APRI and FIB-4 are scoring systems that can be easily calculated using liver transaminases and PLT counts, which are regularly assessed in the follow-up of patients. These scores are recommended in the guidelines for evaluating liver fibrosis in CHB patients [4,16]. A meta-analysis highlighted the importance of FIB-4 in detecting advanced fibrosis and cirrhosis [17]. Zhijian *et al.* [18] reported higher APRI scores in HBeAg-positive CHB patients with advanced fibrosis and inflammation. Furthermore, another study compared AST/ALT ratio, APRI, and FIB-4 scoring and reported that the APRI score had the best diagnostic accuracy for detecting liver fibrosis of any degree [19]. Alavian *et al.* [20] observed that patients with more advanced necroinflammatory activity had higher liver transaminases and APRI scores, alongside lower PLT counts. Zhang *et al.* [8] found higher ALBI grades in patients with HBeAg clearance. It is thought that the albumin and bilirubin values used in ALBI scoring are related to liver function and that a decrease in albumin and an increase in bilirubin may be observed in CHB patients as a result of liver damage related to the immune-active phase. Since it is known that necroinflammatory activity is associated with better treatment response, they interpreted that a higher ALBI grade may be detected in patients with HBeAg loss [8,21]. In light of these data, it was considered that the higher APRI, FIB-4, and FS scores, which are indicators of necroinflammatory disease, and the lower PLT values found in patients with HBeAg loss compared to those without, could be explained by the previously reported relationship between necroinflammatory activity and treatment response.

In contrast to our findings showing no significant association between HBV DNA and ALT levels and HBeAg clearance, several studies have reported the opposite. For example, Zhang *et al.* [8] reported that lower baseline HBV DNA levels and elevated ALT levels have been associated with a higher probability of HBeAg clearance. However, another study found that both baseline HBV DNA and ALT levels were higher in patients who developed HBeAg seroconversion than in those who did not [22]. This inconsistency may be due to differences in study design, population characteristics, or specific antiviral regimens used. The variability in the predictive value of these markers suggests that although HBV DNA and ALT are important factors to consider, they may not consistently predict HBeAg clearance in all patient populations.

Despite the insightful findings of our study, several limitations need to be acknowledged. One limitation is the retrospective, single-center study design that could lead to selection bias and reduce the generalizability of findings to broader populations. Also, with any single-center experience, the treatment protocols may be neither generalizable to other settings nor applicable in different regions or countries. Factors such as comorbidities, hepatitis B virus genotype, and various antiviral treatment regimens used may differentially affect HBeAg clearance. A multicenter approach or prospective studies could help minimize these limitations.

Conclusions

In summary, our study highlights the potential predictive value of factors such as FIB-4, PLT count, and especially APRI, in determining HBeAg clearance in patients undergoing antiviral therapy for HBeAg-positive CHB. APRI, with the highest area under the curve (AUC = 0.771), emerges as the most significant predictor of HBeAg clearance, offering clinicians a reliable marker for assessing the prognosis of chronic hepatitis B and determining the potential for treatment discontinuation. These findings emphasize the importance of using specific biomarkers and scoring systems to guide clinical decisions and optimize treatment strategies for chronic hepatitis B patients. Further validation and research are necessary to confirm these findings and enhance the management of HBeAg-positive CHB.

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Authors' contributions

Conception and Design: Tİ, AÖ, SMÇ; Supervision: İEY, UK, AE; Data collection: Tİ, AÖ, SMÇ; Analyses: Tİ, SMÇ; Literature review: Tİ, İEY, UK, AE; Writing: Tİ, AÖ; Critical review: İEY, UK, AE

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Conflict of interests

No conflict of interests is declared.

References

1. World Health Organization (2024) Hepatitis B key facts. Available: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b. Accessed: 20 May 2024.
2. Lin D, Yang HI, Nguyen N, Hoang J, Kim Y, Vu V, Le A, Chaung K, Nguyen V, Trinh H, Zhang J, Hsing A, Chen CJ, Nguyen MH (2016) Reduction of chronic hepatitis B-related hepatocellular carcinoma with anti-viral therapy, including low risk patients. Aliment Pharmacol Ther 44: 846-855. doi: 10.1111/apt.13774.
3. Moon JC, Kim SH, Kim IH, Lee CH, Kim SW, Lee SO, Lee ST, Kim DG (2015) Disease progression in chronic hepatitis B patients under long-term antiviral therapy. Gut Liver 9: 395-404. doi: 10.5009/gnl14170.
4. Türkiye Karaciğer Araştırmaları Derneği, Viral Hepatitle Savaşım Derneği (2023) Türkiye Hepatitis B Diagnosis and Treatment Guide. Available: https://www.vhsd.org/tr/hepatit-b-klavuzu-2-23_a.html. Accessed: 20 May 2024. [Article in Turkish]
5. European Association for the Study of the Liver (2017) EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 67: 370-398. doi: 10.1016/j.jhep.2017.03.021.
6. Liaw YF (2009) HBeAg seroconversion as an important end point in the treatment of chronic hepatitis B. Hepatol Int 3: 425-433. doi: 10.1007/s12072-009-9140-3.
7. Sarin S, Kumar M, Lau GK, Abbas Z, Chan HLY, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao J (2016) Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 10: 1-98. doi: 10.1007/s12072-015-9675-4.
8. Zhang Y, Gu Y, Yin S, Wang J, Zhang Z, Liu Y, Chen Y, Zhan J, Xue R, Yan X, Zhang S, Ding W, Chen Y, Li J, Huang R, Wu C (2023) Baseline albumin-bilirubin score: a predictor for HBeAg clearance in patients with chronic hepatitis B after nucleos (t) ide analogue treatment. Eur J Gastroenterol Hepatol 35: 1023-1029. doi: 10.1097/MEG.0000000000002598.
9. Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, Heathcote EJ, Manns M, Bzowej N, Niu J, Jan SH, Hwang SG, Cakaloglu Y, Tong MJ, Papatheodoridis G, Chen Y, Brown NA, Albanis E, Galil K, Naoumov NV (2009) 2-Year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. Gastroenterology 136: 486-495. doi: 10.1053/j.gastro.2008.10.026.
10. Peng CY, Hsieh TC, Hsieh TY, Tseng KC, Lin CL, Su TH, Tseng TC, Lin HH, Wang CC, Kao J (2015) HHBV-DNA level at 6 months of entecavir treatment predicts HBeAg loss in HBeAg-positive chronic hepatitis B patients. J Formos Med Assoc 114: 308-313. doi: 10.1016/j.jfma.2013.10.023.
11. Yu W, Wang Y, Shen C, Ji R, Zhang L, Zhao X, Su M, Zhang Y, He W, Cao J, Hao Y, Chen S, Zhao C (2017) Predictors of HBeAg seroconversion after long-term nucleos (t) ide analogues treatment for chronic hepatitis B: a multicenter study in real clinical setting. Braz J Infect Dis 21: 213-218. doi: 10.1016/j.bjid.2017.03.001.
12. Ono A, Suzuki F, Kawamura Y, Sezaki H, Hosaka T, Akuta N, Kobayashi M, Suzuki Y, Saitou S, Arase Y, Ikeda K, Kobayashi M, Watahiki S, Mineta R, Kumada H (2012) Long-term continuous entecavir therapy in nucleos (t) ide-naïve chronic hepatitis B patients. J Hepatol 57: 508-514. doi: 10.1016/j.jhep.2012.04.037.
13. Chu CJ, Hussain M, Lok AS (2002) Hepatitis B virus genotype B is associated with earlier HBeAg seroconversion compared with hepatitis B virus genotype C. Gastroenterology 122: 1756-1762. doi: 10.1053/gast.2002.33588.
14. Buster EH, Hansen BE, Lau GK, Piratvisuth T, Zeuzem S, Steyerberg EW, Janssen HL (2009) Factors that predict response of patients with hepatitis B e antigen–Positive chronic hepatitis B to peginterferon-alfa. Gastroenterology 137: 2002-2009. doi: 10.1053/j.gastro.2009.08.061.
15. Downs LO, Smith DA, Lumley SF, Patel M, McNaughton AL, Mokaya J, Ansari MA, Salih Z, Varnai KA, Freeman O, Cripps S, Philips J, Collier J, Woods K, Channon K, Davies J, Barnes E, Jeffery K, Matthews PC (2019) Electronic health informatics data to describe clearance dynamics of hepatitis B surface antigen (HBsAg) and e antigen (HBeAg) in chronic hepatitis B virus infection. MBio 10: e00699–19. doi: 10.1128/mbio.00699-19.
16. Terrault NA, Lok AS, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown Jr RS, Bzowej NH, Wong JB (2018) Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 67: 1560-1599. doi: 10.1002/hep.29800.
17. Li Y, Chen Y, Zhao Y (2014) The diagnostic value of the FIB-4 index for staging hepatitis B-related fibrosis: a meta-analysis. PloS one 9: e105728. doi: 10.1371/journal.pone.0105728.
18. Zhijian Y, Hui L, Weiming Y, Zhanzhou L, Zhong C, Jinxin Z, Hongyan W, Xiangbin D, Weizhi Y, Duoyun L, Xiaojun L, Qiwen D (2015) Role of the aspartate transaminase and platelet ratio index in assessing hepatic fibrosis and liver inflammation in adolescent patients with HBeAg-positive chronic hepatitis B. Gastroenterol Res Pract 2015: 906026. doi: 10.1155/2015/906026.
19. Moosavy SH, Eftekhar E, Davoodian P, Nejatizadeh A, Shadman M, Zare S, Nazarnezhad MA (2023) AST/ALT ratio, APRI, and FIB-4 compared to FibroScan for the assessment of liver fibrosis in patients with chronic hepatitis B in Bandar Abbas, Hormozgan, Iran. Bmc Gastroenterol 23: 145. doi: 10.1186/s12876-023-02780-w.
20. Alavian SM, Alavian SH, Ashayeri N, Babaei M, Daneshbodi M, Hajibeigi B (2010) Prediction of liver histological lesions with biochemical markers in chronic hepatitis B patients in

Iran. Gastroenterol Hepatol Bed Bench 3. doi: 10.22037/ghfbb.v3i2.82.

21. Brakenhoff SM, De Knegt RJ, Oliveira J, Van Der Eijk AA, Van Vuuren AJ, Hansen BE, Janssen HLA, de Man RA, Boonstra A, Sonneveld MJ (2023) Levels of antibodies to hepatitis B core antigen are associated with liver inflammation and response to peginterferon in patients with chronic hepatitis B. J Infec Dis 227: 113-122. doi: 10.1093/infdis/jiac210.
22. Yang J, Yan D, Guo R, Chen J, Li Y, Fan J, Fu X, Yao X, Diao H, Li L (2017) Predictive value of serum ALT and T-cell receptor beta variable chain for HBeAg seroconversion in chronic hepatitis B patients during tenofovir treatment. Medicine 96: e6242. doi: 10.1097/MD.0000000000006242.