How to evaluate the HbeAg-positive during the natural course of Chronic Hepatitis B in clinic? A cross-sectional study

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Abstract

Background

The previous studies showed the correlation between HBsAg and serum HBV DNA levels was weak or missing.

Objective

The study aims to investigate the correlation between HBeAg and HBV DNA levels, and to find an alternative tool to evaluate the HBV DNA level for clinicians.

Methods

A total of 1020 patients with CHB were enrolled in this cross-sectional study. We divided the patients into four groups as: HBeAg positivity and negativity groups, and high and low HBV DNA levels groups. Further, as per the levels of serum HBV DNA, we performed subgroups’ analyses for the HBeAg-positive and HBeAg-negative groups.

Results

Results showed that the ALT, ALB and HBeAg are independent factors to estimate the serum HBV DNA in CHB patients. But diagnosing the high levels of HBV DNA is not credible (the AUC=0.622, Fig1-A). In HBeAg-positive group, when the level of HBeAg is higher than 16.15 S/CO, we can predict the patient with high levels of HBV DNA (> 2000 IU/ml, AUC=0.787, Fig1-C) and the patients were 4 folds to have the high levels of HBV DNA than the HBeAg-negativ (table3). The levels of ALT and TB are the independent risk factors for the patients in HBeAg-negative group. When the levels of ALT and TB are higher 36.5 IU/L and 11.15 umol/L, respectively, the patient would have a high levels of HBV DNA (> 2000 IU/ml, AUC=0.609, Fig2-B).

Conclusion

HBeAg is an independent factor that reflects the levels of serum HBV DNA with a strong correlation, but it is not accurate to evaluate the levels of serum HBV DNA by the HBeAg-
positive. On the other hand, the patients with HBeAg-negative are not mean having a low levels of HBV DNA, which can be evaluated by the levels of ALT and TB.

Background

Hepatitis B virus (HBV) infection is a serious public health problem worldwide. Previous studies have shown that approximately one-third of the world’s population has HBV infection, and this infection is responsible for approximately 500,000 deaths annually, and over 350 million people facing been affected [1,2]. Further, HBV infection can cause acute or chronic hepatitis, cirrhosis, hepatic decompensation, and hepatocellular carcinoma [3]. Generally, the natural course of CHB includes several phases as follows: I) I) immune tolerance phase (IT), with hepatitis B e antigen positivity (HBeAg [+]), high HBV-DNA levels, and normal levels of alanine aminotransferase (ALT), I) immune clearance phase (IC), with HBeAg (+), high HBV DNA levels, normal or high ALT levels, III) low-replicative phase (LR), with HBeAg-negativity [HBeAg (−)], hepatitis B e antibody positivity (HbeAb [+]), undetectable levels of HBV DNA and normal ALT levels, iv) HBeAg-negative hepatitis (ENH), with HBeAg (−), HbeAb (+), high HBV DNA and ALT levels [4-7]. HBV DNA is a risk factor for liver cirrhosis as per Illoeje UH, Yang HI, et al. reported[8] HBV DNA with the levels of $10^4$ - $10^5$ copies/mL (2000-20000 IU/mL), $10^5$ - $<10^6$ copies/mL (20000-200000 IU/mL) and $>10^6$ copies/mL(200000 IU/mL), the risks to develop into liver cirrhosis are 2.5, 5.6 and 6.5 folds, respectively.

Testing the HBV DNA of the serum is a common method of evaluating the effect of treatment decisions on patients and assessing the response to antiviral therapy [9,10]. Previous studies have reported a correlation between the HBsAg and HBV DNA levels and have suggested [6,11-14] serum HBsAg quantitation can be a marker to predict HBV DNA levels. However, similar studies have shown no correlations of HBsAg with HBV DNA [15-
16]. Research trials have tested the quantification of serum HBsAg accurately, which is difficult in clinic to test the quantification of serum HBeAg in our center, especially, Gupta E, Kumar A, et al.[11] reported that the best cut-off point of serum HBsAg quantification to predict the high HBV DNA levels is $3.36 \times 10^3$ IU/ml. However, when the HBsAg level is >3000 IU/mL in our center, the results were shown to be >3000 IU/mL. Thus, HBsAg quantification is difficult to apply in the clinical setting, and the correlation with HBV DNA is weak or absent. In contrast, the HBV DNA levels are not exactly similar with the natural course of CHB. Generally, the patients with HBeAg positivity (IT phase or IC phase) have high levels of serum HBV DNA. However, in the clinical setting, the levels of serum HBV DNA remain undetected in some patients. Patients with HBeAg-negativity (LR phase and HBeAg-negative hepatitis phase) are believed to have low HBV DNA levels. However, a survey of HBeAg-negative patients showed that 47.5% of the patients in LR phase and 63.4% in the HBeAg-negative hepatitis phase had high serum HBV DNA levels ($> 10^4$ copies/mL) [17]. Thus, HBV DNA levels are high or undetected in both, HBeAg-positive and HBeAg-negative, patients. This phenomenon poses a challenge to clinicians, regarding whether and when we should recommend a HBV DNA test for patients with CHB, because HBV DNA testing is expensive, and there is insufficient evidence to convince the patient. Therefore, there is a need for an alternative tool to evaluate the levels of HBV DNA easily in CHB.

HBeAg plays a crucial role in HBV infection, meaning the high replication and high infectivity of CHB [18], but it has not been reported the correlation with HBV DNA in previous studies. This study aimed to determine the correlation between HBeAg and HBV DNA, to evaluate the difference between HBeAg-positive and HBeAg-negative patients, and to find an alternative tool to serum HBV DNA levels in CHB patients to establish
whether to have a serum HBV DNA test.

Methods

1.1 Patients
We retrospectively evaluated HBV patients who underwent serum HBV and HBV-DNA tests at our center, in the Department of Liver Surgery, Liver Transplantation Center, West China Hospital of Sichuan University, from 2011 to 2013. The criteria for patient inclusion were as follows: i) Age > 18 years, ii) first visit to our center, and iii) positivity in HBsAg and HBeAg, or positive with HBsAg on serum HBV test. Patients were excluded when they had i) co-infection with other hepatitis viruses, such as hepatitis C, A, and D; ii) had acute hepatitis, especially acute liver failure; or iii) had received antiviral treatment at other hospitals. According to previous studies [7,8,11], high HBV DNA level is defined to be >2000 IU/mL.

1.2 Methods
We divided the patients into four groups as per HBeAg positivity and negativity, high and low HBV DNA levels, respectively. Further, as per the levels of serum HBV DNA, we performed subgroup analyses for the HBeAg-positive and HBeAg-negative groups.

1.3 Statistical analysis
All the data were analyzed using SPSS 22.0 data statistical software (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation (± sd) values. Between-group comparisons of the continuous variables were made using T-test, and the optimal predictive cut-off value was determined by Receiver Operating Characteristics (ROC) curves. Using logistic regression multivariate analysis to identify the independent risk and getting a model predict. The categorical variables were analyzed using chi-square test \( (c^2) \). For all the analyses, P value < 0.05 was considered statistically significant.
Results

2.1 Comparison between HBeAg (+) and HBeAg (−) patients

We enrolled 1020 patients in this study from January 2011 to December 2013, including 881 males and 139 females; 252 patients were HBeAg-positive (HBeAg [+]) and 768 were HBeAg-negative (HBeAg [−]); 535 had high serum HBV DNA; and 585 had low serum HBV DNA levels. The characteristics of the patient groups are shown in table 1. The values of age, the platelet count (PLT), aspartate aminotransferase (AST), and HBV DNA levels are significant between the groups of HBeAg-positive and HBeAg-negative patients. The HBeAg-positive group was younger, had lower PLT levels, and had higher AST levels than the HBeAg-negative group. In contrast, the white blood cell (WBC) count and the levels of hemoglobin (HGB), total bilirubin (TB), alanine aminotransferase (ALT), albumin (ALB), and prothrombin time did not differ significantly. From figure 1-A, judging the serum HBV DNA levels based on HBeAg-positivity with the AUC was 0.622.

2.2 Different HBV DNA levels in CHB

Table 1 shows the feature of high HBV DNA levels and low HBV DNA levels of the whole course of natural CHB. The continuous variables of PLT, AST, ALT, and ALB were significantly different between the high HBV DNA group and the low HBV DNA group, with the ROC shown in figure 1-B. The AUC of AST, ALT, ALB, and PLT was 0.635, 0.642, 0.432, and 0.473, respectively, and the optimal cutoff points were 46.5 IU/L, 42.5 IU/L, 25.5 g/L, and 74.5 × 10⁹/L, respectively. The levels of AST and ALT were higher in high HBV DNA group, and the levels of PLT and ALB were lower than low HBV DNA group. However, the logistic regression multivariate analyses showed no significance in the PLT and AST. Through the logistic regression multivariate analysis and univariate analysis, the independent factors to evaluate the levels of HBV DNA are ALT, ALB and HBeAg (table 3).
Based on the results, we drew the following predictive model:

\[ Y_1 \text{ (high HBV DNA levels) } = 1.412 \times (1 \text{ for HBeAg-positive or 0 for others}) + 0.004 \times (1 \text{ for ALT > 42.5 U/L or 0 for others}) - 0.029 \times (1 \text{ for ALB > 25.5 g/L or 0 for others}) + 0.779 \]

The ROC of the predictive model \( Y_1 \) is shown in figure 2-A. The AUC is 0.606, and the cutoff value is 0.752.

### 2.3 HBV DNA levels in HBeAg (+) patients

A comparison of the HBeAg-positive patients with high and low HBV DNA levels were shown in table 2. The sex, age, PLT, WBC, TB, AST, and ALT were not significantly different. The variables of HGB, ALT, and HBeAg were significant in the univariate and multivariate analyses; the AUC was 0.394, 0.379, and 0.787, respectively, with the optimal cutoff points being 170.5 g/L, 25.0 g/L, and 16.15 S/CO, respectively, (Figure 1-C).

### 2.4 HBV DNA levels in HBeAg (−) patients

Table 2 summarizes the HBV DNA levels characteristics of CHB in HBeAg-negative patients. The variables of TB, AST, and ALT were significantly different between the two groups as per univariate analysis. The AUC of these three variables was 0.511, 0.628, and 0.655, respectively (figure 1-D), and the cutoff values were 11.15 umol/L, 36.5 U/L, and 42.5 U/L, respectively. However, in the logistic regression multivariate analyzes, only TB and ALT were significant, as shown in table 3. Following the result, we can draw another predictive model of HBV DNA levels in the HBeAg-negative patients with CHB:

\[ Y_2 \text{ (low levels of HBV DNA) } = 0.385 - 0.005 \times (1 \text{ for ALT > 36.5 IU/L or 0 for others}) - 0.006 \times (1 \text{ for TB > 11.15 umol/L or 0 for others}) \]

The ROC of the predictive model \( Y_2 \) is shown in figure 2-B. The AUC was 0.609, and the cutoff value was 0.3765.

Discussion
HBV DNA is a marker of antiviral treatment response and high infectivity in CHB. The different phases of the natural course of CHB have their own's specific characteristics, and we cannot judge the levels of serum HBV DNA as per the course of CHB [17]. Previous studies have shown a weak or absent correlation between HBsAg and HBV DNA levels [11-16]. To our knowledge, few studies have assessed the correlation between HBeAg and serum HBV DNA. A survey carried by Ping Chen, Qinfen Xie, et al. [30] showed the highest levels serum HBV DNA ( > 10⁷ copies/mL) with 768 S/CO of the HBeAg level, which could indicate the relation of HBV DNA level in IT phage. In the current study analyzed the whole course of CHB in clinic. The results are shown in table 1. The HBeAg-positive patients were younger than the HBeAg-negative patients (p<0.001, table 1), however, the age in the serum HBV DNA levels group were not significantly difference (p=0.394, table 1). This may reflect the natural course of CHB in the different phases of life. The patients in different stages of life acquisition of the virus show differences in the behavior of HBeAg in the clinical setting. For example, when a patient is infected at birth or at 1–2 years of age, they experience a prolonged IC phase. In contrast, infected after early children, the patients generally do not experience the IT phase, they will enter the LR phage quickly. And the levels of serum HBV DNA did not mean low [19]. So the age is not a reasonable factor to predict the serum HBV DNA of patients with HBeAg-positive.

The PLT count is different between the HBeAg-positive and HBeAg-negative patients as well as those with high and low levels of serum HBV DNA (p₁=0.001 and p₂=0.011, table 1). However, in subgroups’ analyses showed a non-significant difference (p₁=0.739 and p₂=0.086, table 2). An animal model has suggested a link between the PLT count and immune control of HBV infection [20,21]. The model analyzed the whole natural course of the CHB, so when we divided the situation into two groups: i) the PLT count in HBeAg-
positive and HBeAg-negative group; ii) the PLT count in high or low HBV DNA levels group. We can find that the PLT is significant difference between HBeAg-positive versus HBeAg-negative groups (121.6 vs 140.81, p=0.001, table 1), and the high serum HBV DNA levels versus the low serum HBV DNA groups (129.84 vs 142.87, p=0.011, table 1), but the levels of PLT count is in the normal range, which can’t convey a useful information to identify the levels of serum HBV DNA. Further, the multivariate analyses also eliminates the PLT count to predict the serum HBV DNA. Therefore, the correlation between PLT and HBV DNA level needs further research.

The level of ALT is very important in CHB patients because it is a marker of liver function damage. The natural course of CHB is based on biochemical, serological, and virological characteristics, including serum ALT levels, HBeAg serostatus, and HBV DNA levels [4-7]. Some studies have pointed out that although the level of AST is normal, the levels of serum HBV DNA need to be tested [22,23]. On the other hand, the high AST levels may be associated with HBV replication throughout the course of chronic HBV infection that do harm to the liver [24]. Combining with the multivariate analysis, the levels of ALT is an independent factor to predict the levels of serum HBV DNA, but the odds ratio (OR) are 1.004 and 1.005 in natural course of HBV and the patient with HBeAg-negative, respectively (table 3). The correlation is weak, especially for the patient in HBeAg-positive group, because the HBeAg-positive has a strong correlation of HBV DNA (OR is 4.104, table 3). However, the levels of ALT as a factor to predict the levels of serum HBV DNA in HBeAg-negative group is credible, as to AUC is 0.655 (figure 1-D) and there is no a strong factor in this group. There are also some questions that several studies have reported that the AST levels may vary with body mass index, abnormal lipid and carbohydrate metabolism, and the time of the day [25,26]. We need to pay attention to these factors while evaluating the HBV DNA levels of HBeAg-negative patient with CHB.
Previous studies have reported a weak or absent correlation between HBsAg levels and HBV DNA levels [11-16]. The serum HBsAg levels were higher in the HBeAg-positive patients than in the HBeAg-negative patients [6,24]. HBeAg can be as a sign of the high replication and infectivity of CHB [17]. According to HBeAg-positive to diagnose the high levels of serum HBV DNA is not accurate, because the AUC of ROC is just 0.622 (figure 1-A), which is less than 0.7 (an AUC < 0.7 indicates poor diagnostic ability). However, combining with logistic regression multivariate analysis, HBeAg is an independent factor for the natural course of HBV to predict the levels of serum HBV DNA with an OR of 4.104, meaning that HBeAg-positive patients are 4 times more likely to have high HBV DNA levels than HBeAg-negative patients. Following the predictive model Y_1, HBeAg-positive patients are likely to have a high level of serum HBV DNA. Through the analysis of serum HBV DNA in HBeAg-positive group (table 2), the best cut-off point of HBeAg levels is 16.15 S/CO, meaning those patients with a level of HBeAg higher than 16.15 copy/mL are more likely to have high levels of serum HBV DNA than those not (the AUC is 0.787, Fig 1-C).

HBeAg-negativity with CHB is usually correlated with lower intrahepatic cccDNA levels [27-29]. Therefore, the serum HBV DNA levels are different between HBeAg-positive and HBeAg-negative patients. Lai CL, Ratziu V, et al. [19] reported that HBeAg-negative patients didn’t mean the levels of serum HBV DNA is low. With the analysis of logistic regression multivariate analyses, the independent factors to predict the serum HBV DNA in HBeAg-negative are the levels of TB and ALT, and the cut-off values are 11.15 umol/L and 36.5 IU/L, respectively (table 2). Following the predict model (Y_2), both of TB and ALT are higher than 11.15 umol/L and 36.5 IU/L, respectively, the levels of serum HBV DNA should undergo a test, though the levels of TB and ALT are in normal range, which is contradict with phages of low-replicate and HBeAg-negative hepatitis [5-8]. On the other hand, the HBV infection is throughout the all phages, we can not judge the effectivity of
the levels of HBV DNA just by HBeAg-negative.

The present study has the following limitations: i) cross-sectional retrospective studies need a long-term follow-up to identify the parameters that reflect the response of patients who had received the antivirus treatment, especially those who had high levels of serum HBV DNA and were HBeAg-positive. In the current study, we did not perform follow-up to study the effect of antiviral treatment ii) We did not divide the patients into different phases as per the natural course of CHB. We studied the entire cohort of CHB patients; this might not reflect the real levels of serum HBV DNA in HBeAg-negative patients iii) The levels of serum HBV DNA may be different between HBV-genotype A and D; we did not assess the HBV-genotype in the patients.

In conclusion

HBeAg is an independent factor that reflects the levels of serum HBV DNA with a strong correlation, but it is not accurate to evaluate the levels of serum HBV DNA by the HBeAg-positive. On the other hand, the patients with HBeAg-negative are not mean having a low levels of HBV DNA, which can be evaluated by the levels of ALT and TB.

Abbreviations

HBsAg: Hepatitis B surface antigen, HBeAg : Hepatitis B ‘e’ antigen, HBeAb : Hepatitis B ‘e’ antibody, CHB: Chronic Hepatitis B, HBV: Hepatitis B virus; HGB : Hemoglobin, PLT : Platelet, WBC : White blood cell, TB : Total bilirubin, AST : Aspartate aminotransferase, ALT : Alanine aminotransferase, ALB : Albumin, PT : Prothrombin time.

Declarations

Ethics

This study was approved by the West China Hospital Ethics Committee, and in accordance with the ethical guidelines of the Declaration of Helsinki.
Consent for publication

Not applicable.

Availability of data and materials

The data sets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author’s contribution

Author Contributions: Study conception and design: Li Jiang; Acquisition of data: Jinli Zheng; Analysis and interpretation of data: Li Jiang; Drafting of manuscript: Yang Huang, Jinli Zheng; Critical revision: Li Jiang; Lingpeng Yang and Jinli Zheng contributed in statistical analysis.

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Tables

Table 1. The characteristic of the whole natural course of CHB

| Variable                  | HBeAg (+) | HBeAg (-) | P1 value | Serum HBVDNA Levels | P2 value |
|---------------------------|-----------|-----------|----------|---------------------|----------|
| Sex (male/female)         | 223/29    | 658/110   | 0.258    | 474/61              | 0.03*    |
| Age (years)               | 46.49±10.47 | 52.12±12.03 | <0.001* | 50.42±11.29         | 51.05±12.56 | 0.394 |
| HGB (g/L)                 | 135.63±23.09 | 134.90±21.60 | 0.650    | 134.46±22.88        | 135.78±21.02 | 0.34  |
| PLT (×10^9/L)             | 121.60±76.57 | 140.81±82.09 | 0.001*  | 129.84±70.75        | 142.87±90.80 | 0.011* |
| WBC (×10^9/L)             | 5.48±3.38  | 5.91±3.42  | 0.083    | 5.66±3.23           | 5.95±3.60  | 0.184 |
| TB (umol/L)               | 25.94±53.78 | 25.37±51.48 | 0.878    | 23.18±45.26         | 28.09±58.7 | 0.133 |
| AST (IU/L)                | 94.77±134.41 | 70.25±82.53 | 0.001*  | 86.41±109.85        | 65.29±83.15 | 0.001* |
| ALT (IU/L)                | 68.62±88.39 | 59.18±62.46 | 0.062    | 69.26±77.35         | 53.00±59.57 | <0.001 |
| ALB (g/L)                 | 38.42±7.51  | 39.21±5.63  | 0.080    | 38.46±6.56          | 39.62±5.63  | 0.003* |
| PT (s)                    | 12.87±2.35  | 12.71±2.30  | 0.362    | 12.84±2.19          | 12.65±2.44  | 0.177 |
| HBV-DNA levels (>2×10^3 IU/ml/<2×10^3 IU/ml) | 194/58 | 341/427 | <0.001* | -                   | -             |
| HBeAg(+) / HBeAg (-)     | -          | -          | -        | 194/341             | 58/427     | <0.001 |
HBeAg : Hepatitis B ‘e’ antigen, HBeAb : Hepatitis B ‘e’ antibody, HGB : Hemoglobin, PLT : Platelet, WBC : White blood cell, TB : Total bilirubin, AST : Aspartate aminotransferase, ALT : Alanine aminotransferase, ALB : Albumin, PT : Prothrombin time.

Table 2. the different HBV DNA in HBeAg(+) and HBeAg(-)

|                      | HBeAg(+) | HBeAg(-) | P1 value | Cut-off point | HBeAg(+) | HBeAg(-) | P2 value | Cut-off point |
|----------------------|----------|----------|----------|--------------|----------|----------|----------|--------------|
| Sex (male/female)    | 172/22   | 51/7     | 0.879    | -            | 302/49   | 356/71   | 0.305    | -            |
| Age (years)          | 46.82±1  | 45.44±9  | 0.378    | -            | 52.46±1  | 51.82±1  | 0.463    | -            |
| HGB (g/L)            | 133.71±23.94 | 142.09±18.19 | 0.015    | 170.5        | 134.89±22.27 | 134.93±21.25 | 0.979    | -            |
| PLT (×10^9/L)        | 120.67±72.38 | 124.53±90.49 | 0.739    | -            | 135.09±69.37 | 145.36±90.66 | 0.086    | -            |
| WBC (×10^9/L)        | 5.47±3.2  | 5.52±3.7 | 0.912    | -            | 5.78±3  | 6.00±3.5 | 0.359    | -            |
| TB (umol/L)          | 27.51±6  | 21.04±5  | 0.425    | -            | 20.71±6 | 29.05±6 | 0.026    | 11.15        |
| AST (IU/L)           | 101.48±141.86 | 73.78±106.62 | 0.170    | -            | 77.81±85.51 | 64.13±7.95 | 0.022    | 42.5         |
| ALT (IU/L)           | 71.29±9  | 60.36±5  | 0.411    | -            | 68.10±64.78 | 52.00±5.94 | 0.001    | 36.5         |
| ALB (g/L)            | 37.88±7.64 | 40.23±6.37 | 0.036    | 25.0         | 38.79±5.75 | 39.54±5.52 | 0.068    | -            |
| PT (s)               | 12.98±2.52 | 12.49±1.62 | 0.173    | -            | 12.77±1.96 | 12.67±2.53 | 0.556    | -            |
| HBeAg levels (S/CO)  | 138.00±238.74 | 24.46±132.97 | 0.001    | 16.15        | -        | -        | -        | -            |

Table 3. The results of the logistic regression multivariate analysis
| Variable | B    | P       | Exp(B) | Exp(B) 95% CI |
|---------|------|---------|--------|---------------|
|         |      |         |        | Down | Up   |
| ALT     | 0.004| 0.002   | 1.004  | 1.002 | 1.007 |
| ALB     | -0.029 | 0.010 | 0.971  | .950 | 0.993 |
| HBeAg(+) | 1.412 | <0.001 | 4.104  | 2.941 | 0.5726 |
| Constant | 0.779 | 0.035   | 2.178  | -    | -    |
| HBeAg(-) |      |         |        |       |      |
| TB      | -0.006 | 0.008 | 0.994  | 0.989 | 0.998 |
| ALT     | 0.005 | <0.001 | 1.005  | 1.003 | 1.008 |
| Constant | -0.385 | 0.001 | 0.680  | -    | -    |

CHB : Chronic Hepatitis B, HBeAg(-): Hepatitis B ‘e’ antigen negative, B : Partial regression coefficient value, Exp (B) : Odds Ratio (OR), CI: confidence interval.
A: The ROC of judging the HBV DNA levels by HBeAg-positive of the patients with CHB, and the AUC is 0.622. B: The ROC of significant factors in different levels of HBV DNA. These factors are AST, ALT, ALB and PLT, and the AUC 0.635, 0.642, 0.432 and 0.473, respectively. The best cut-off value is 46.5 IU/L, 42.5 IU/L, 25.5 IU/L and $74.5 \times 10^9$ /L respectively. C: The ROC of HBeAg, ALB and HGB in CHB with HBeAg-positive, and the ACU of HBeAg, ALB and HB are 0.787, 0.379 and 0.394 respectively. The best cut-off value of HBeAg is 16.15 S/CO. D: The ROC of TB, AST and ALT in the patients with HBeAg-negative, the AUC and cut-off value are 0.511, 0.628, 0.655 and 11.15 umol/L, 42.5 IU/L, 36.5 IU/L, respectively.
Figure 2

A: Different HBV DNA levels in CHB. The ROC of predict model Y1 (high HBV DNA level), the ACU and best cut-off value are 0.606 and 0.752, respectively. B: The HBV DNA levels in HBeAg-negative. The ROC of predict model Y2 (low HBV DNA level in HBeAg(-)), the AUC and cut-off value are 0.609 and 0.376, respectively.