A predict model to evaluate the HbeAg-positive of Chronic Hepatitis B in clinic: a cross-sectional study

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Research

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Abstract

Background: The previous studies showed the correlation between HBsAg and serum HBV DNA levels were 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: We enrolled 1020 patients in this cross-sectional study. We divided the patients into four groups as: HBeAg positivity and negativity groups, high and low HBV DNA levels groups. Further, as to the levels of HBV DNA, we performed subgroups' in 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. When the level of HBeAg is higher than 16.15 S/CO, predicting the patient with high levels of HBV DNA and 4 folds to have the high levels of HBV DNA than the HBeAg-negativ. The levels of ALT and TB are the independent risk factors in HBeAg-negative group.

Conclusion: HBeAg is an independent factor that reflects the levels of serum HBV DNA with a strong correlation, and we draw a predict model to evaluate the HBV DNA levels as: Y_1 (high HBV DNA levels) = 1.412 × (1 for HBeAg-positive >16.15 S/CO or 0 for others) + 0.004 × (1 for ALT > 42.5 U/L or 0 for others) −0.029 × (1 for ALB > 25.5 g/L or 0 for others) + 0.779. For the patients with HBeAg(-), we should evaluate by the levels of ALT and TB, and the predict model is:Y_2 (low levels of HBV DNA) = 0.385 − 0.005 × (1 for ALT > 36.5 IU/L or 0 for others) − 0.006 × (1 for TB > 11.15 umol/L or 0 for others).

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 following: I) I) immune tolerance phase (IT), with hepatitis B e antigen positivity (HBeAg [+]), high HBV-DNA levels, and normal levels of alanine aminotransferase (ALT). II) 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 Iloeje 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 levers is a common method to evaluate the effect of treatment decisions on patients and assess 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 to reflect the HBV DNA levers. 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 3.36×10^3 IU/ml, however, it is difficult to identify the quantification of serum HBeAg in clinic. Thus, HBsAg quantification test is difficult to apply in the clinical setting, and the correlation with HBV DNA is weak or absent[15–16]. In contrast, the HBV DNA levels are not exactly similar with the natural course of CHB. In clinic, the patients with HBeAg positivity (IT phase or IC phase) have high levels of serum HBV DNA, however, some patients with a low HBV DNA levels. 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 with high HBV DNA levels ($> 10^4$ copies/mL) [17]. Thus, HBV DNA levels are high or undetected in both patients, HBeAg-positive and HBeAg-negative. This phenomenon poses a challenge to clinicians, regarding whether we should recommend a HBV DNA test for patients with CHB, because HBV DNA test is expensive, and it is insufficient evidence to convince the patient to have a HBV DAN test. Therefore, it needs an alternative tool to evaluate HBV DNA levels roughly for providing an evidence to persuade the people to have a HBV DNA test.

HBeAg plays a crucial role in HBV infection, meaning the high replication and high infectivity of CHB [18], and it has a strong correlation with HBV DNA in previous studies. This study aims to compare the difference between HBeAg-positive and HBeAg-negative patients, and to find an alternative tool to evaluate the HBV DNA levels.

1. Materials And Methods

1.1 Patients

We enrolled the patients at our center, the department of Liver Surgery and Liver Transplantation Center, West China Hospital of Sichuan University, from 2011 to 2013. The criteria wsa as following: 1) Age > 18 years, 2) having HBV DNA test in our center, and 3) positivity in HBsAg and HBeAg, or only positive with HBsAg on serum HBV test. Patients were excluded when they met one of the criteria: 1) co-infection with other hepatitis viruses, such as hepatitis C, A, and D; 2) acute hepatitis, especially acute liver failure; and 3) had received antivirus treatment at other centers.

According to previous studies [7,8,11], high HBV DNA level is defined as >2000 IU/mL.

1.2 Methods

We divided the patients into four groups as: HBeAg positivity group and HBeAg negativity group, high HBV DNA levels group and low HBV DNA levels group. Further, 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 ($\bar{x}$ ± sd) values. Between-group comparisons of the continuous variables were made using T-test or W-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.

2. Results

2.1 Characteristic of 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 HBV DNA levels and 585 had low HBV DNA levels. The characteristics of the patients was shown in table 1. The values of age, the platelet count (PLT), aspartate aminotransferase (AST), and high HBV DNA levels are significant between the patients of HBeAg(+) and HBeAg(-) . The HBeAg(+) patients was younger, lower PLT levels, and higher AST levels than the HBeAg(-) patients. 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 high HBV DNA levels based on HBeAg(+) might be reliable, for the AUC (area of under the curve) was 0.622.

2.2 Characteristic in different HBV DNA levels

Table 1 shows the feature of high HBV DNA levels and low HBV DNA levels. The difference of PLT, AST, ALT, and ALB were significant between the high HBV DNA group and the low HBV DNA group, and the ROC was 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 74.5×10^9/L, respectively. The levels of AST and ALT were higher in high HBV DNA group, and the levels of PLT and ALB were lower. Furthermore, 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 are ALT, ALB and HBeAg (table 3). We drew the following predictive model of high HBV DNA levels as:

Y_1 (high HBV DNA levels) = 1.412 × (1 for HBeAg-positive >16.15 S/CO or 0 for others) + 0.004 × (1 for ALT > 42.5 U/L or 0 for others) −0.029 × (1 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 The different HBV DNA levels in HBeAg (+) patients

The comparison of the HBeAg(+) 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, and the AUC was 0.394, 0.379, and 0.787, respectively, with the optimal cut-off points being 170.5 g/L, 25.0 g/L, and 16.15 S/CO, respectively, (Figure 1-C).

2.4 The different HBV DNA levels in HBeAg (-) patients

Table 2 summarizes the HBV DNA levels characteristics of CHB in HBeAg(-) 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 showing in table 3. Following the result, we can draw another predictive model of HBV DNA levels in the HBeAg(-) patients:

Y_2 (low levels of HBV DNA) = 0.385 − 0.005 × (1 for ALT > 36.5 IU/L or 0 for others) − 0.006 × (1 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 antivirus 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 (> 10^7 copies/mL) with 768 S/CO of the HBeAg level, which could indicate the relation of HBV DNA levels in IT phage. In the current study analyzed the whole course of CHB in clinic. The results are shown in Table 1. The HBeAg(+) patients were younger than the HBeAg(-) patients ($p < 0.001$, Table 1), however, the age in the serum HBV DNA levels group were not significant difference ($p = 0.394$, Table 1). The patients in different stages of life acquisition of the virus would show differences in the behavior of HBeAg. The previous study[19] shew that when a patient is infected at birth or at 1–2 years of age, they experienced 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. 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(+) and HBeAg(-) patients as well as those with high and low levels of serum HBV DNA ($p_1 = 0.001$ and $p_2 = 0.011$, Table 1). However, in subgroups' analyses showed a non-significant difference ($p_1 = 0.739$ and $p_2 = 0.086$, Table 2). An animal model has suggested a link between the PLT count and immune control of HBV infection [20, 21]. This model analyzed the whole natural course of the CHB, so when we divided the situation into two groups: 1) the PLT count in HBeAg(+) and HBeAg(-) group; 2) the PLT count in high HBV DNA levels and low HBV DNA levels group. We can find that the PLT is significant difference between HBeAg(+) versus HBeAg(-) groups (121.6 vs 140.81, p = 0.001, Table 1), and the high 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 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 ALT 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(-), respectively (Table 3). The correlation is weak, especially for the patient in HBeAg(+) group, because the HBeAg(+) has a strong correlation of HBV DNA (OR = 4.104, Table 3). On the other hand, the levels of ALT as a factor to predict the levels of HBV DNA in HBeAg(-) group is credible, as to AUC is 0.655 (Fig. 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(-) 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(+) patients than in the HBeAg(-) patients [6, 24], but as the previous studies reported that the level of HBsAg higher than 3000 IU/ml was a reference for predicting the high HBV DNA level, which wasn't convenient for clinicians. HBeAg can be as a sign of the high replication and infectivity of CHB [17]. In our research, we found that according to HBeAg levlels to predict the high HBV DNA levels is reliable, because the AUC of ROC was 0.622 (Fig. 1-A), and when the HBeAg levels higher than 16.15 S/CO was 4 times to have a high HBV DNA levels than those not. Following the predictive model Y_1 (high HBV DNA levels) = 1.412 × (1 for HBeAg-positive > 16.15 S/CO or 0 for others) + 0.004 × (1 for ALT > 42.5 U/L or 0 for others) − 0.029 × (1 for ALB > 25.5 g/L or 0 for others) + 0.779, and the cut-off value was 0.752. We can explain as the HBeAg(+) patients are likely to have a

high level of serum HBV DNA, but when the levels of HBeAg is lower than 16.15 S/CO, we should combine with ALB and AST to evaluate the high HBV DNA levels (table 2).

HBeAg(-) is usually correlated with lower intrahepatic cccDNA levels [27–29]. Therefore, the serum HBV DNA levels are different between HBeAg(+) and HBeAg(-) patients. On the other hand, Lai CL, Ratziu V, et al. [19] reported that HBeAg(-) 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(-) 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 (Y_2 (low levels of HBV DNA) = 0.385 − 0.005 × (1 for ALT > 36.5 IU/L or 0 for others) − 0.006 × (1 for TB > 11.15 umol/L or 0 for others), and the cutoff value was 0.3765. We find that when the levels of TB and ALT are higher than 11.15 umol/L and 36.5 IU/L, together, the patients should have a HBV DNA test. Though the levels of TB and ALT are in normal range, which is contradict with phages of low-replicate with HBeAg(-) hepatitis [5–8]. On the other hand, the HBV infection is throughout the all phages, we can not ignore the levels of HBV DNA in HBeAg(-) patients.

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.

Conclusion

HBeAg is an independent factor that reflects the levels of serum HBV DNA with a strong correlation, and we draw a predict model to evaluate the HBV DNA levels as: Y_1 (high HBV DNA levels) = 1.412 × (1 for HBeAg-positive > 16.15 S/CO or 0 for others) + 0.004 × (1 for ALT > 42.5 U/L or 0 for others) − 0.029 × (1 for ALB > 25.5 g/L or 0 for others) + 0.779. For the patients with HBeAg(-), we should evaluate by the levels of ALT and TB, and the predict model is:Y_2 (low levels of HBV DNA) = 0.385 − 0.005 × (1 for ALT > 36.5 IU/L or 0 for others) − 0.006 × (1 for TB > 11.15 umol/L or 0 for others).

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 and Yunfeng Zhu; Analysis and interpretation of data: Li Jiang and Jinli Zheng; Drafting of manuscript: Jinli Zheng; Critical revision: Li Jiang; Yunfeng Zhu and Jinli Zheng contributed in statistical analysis.

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Tables

Due to technical limitations, all table files are only available for download from the Supplementary Files section.

Figures

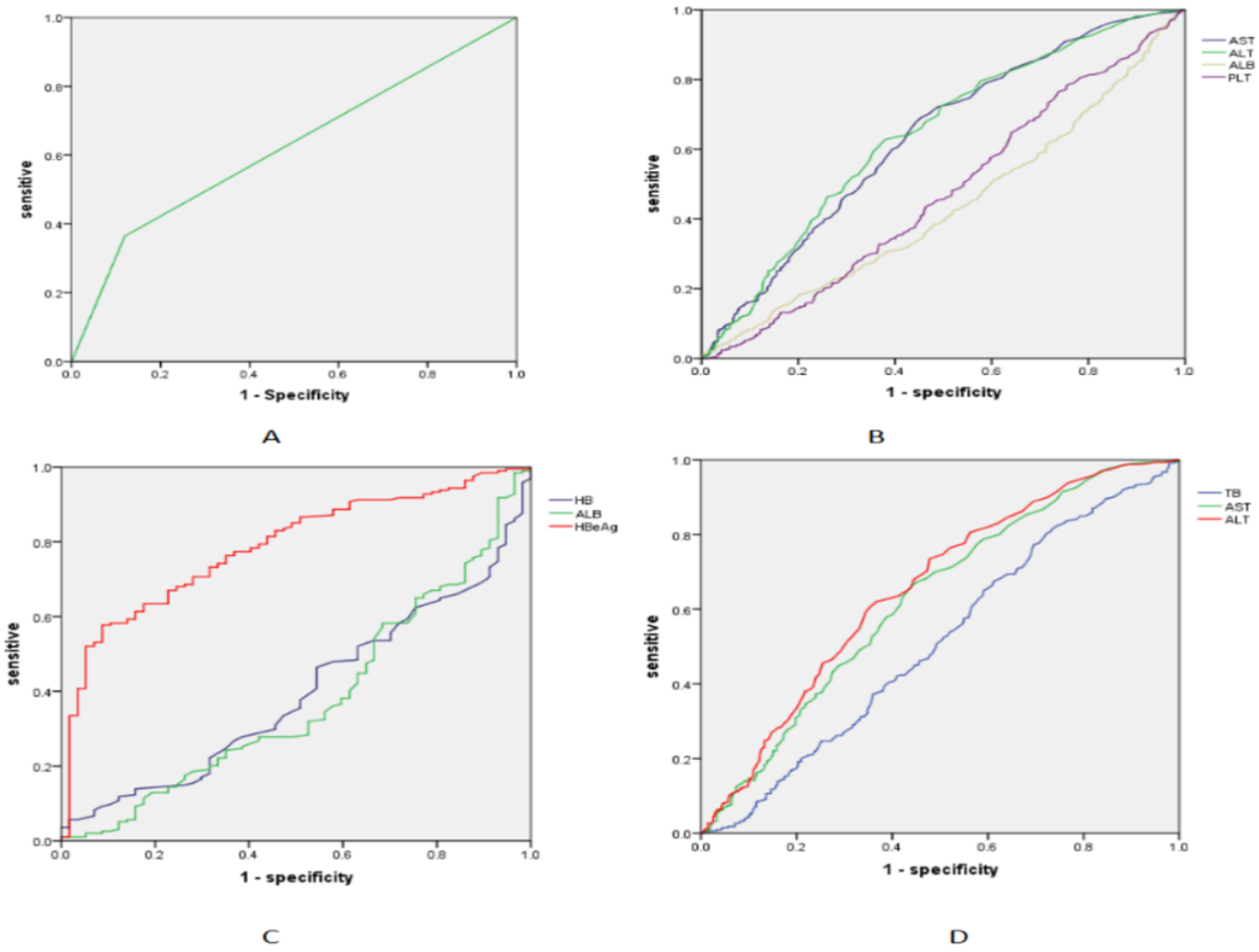

Figure 1

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 × 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.

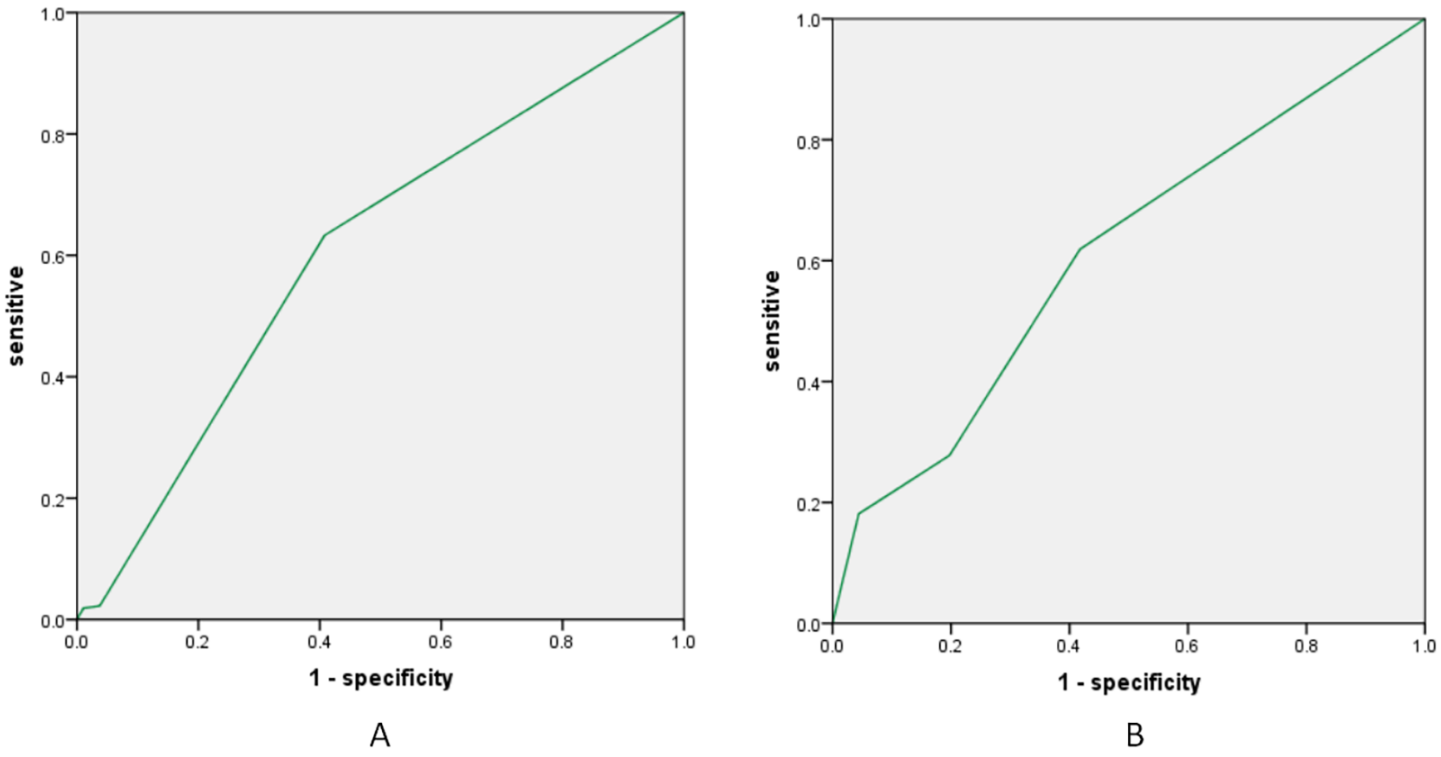

Figure 2

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.

Supplementary Files

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