Precise prediction model and simplified scoring system for sustained combined response to interferon-α

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Abstract

AIM: To establish a predictive algorithm which may serve for selecting optimal candidates for interferon-α (IFN-α) treatment.

METHODS: A total of 474 IFN-α treated hepatitis B virus e antigen (HBeAg)-positive patients were enrolled in the present study. The patients’ baseline characteristics, such as age, gender, blood tests, activity grading (G) of intrahepatic inflammation, score (S) of liver fibrosis, hepatitis B virus (HBV) DNA and genotype were evaluated; therapy duration and response of each patient at the 24th wk after cessation of IFN-α treatment were also recorded. A predictive algorithm and scoring system for a sustained combined response (CR) to IFN-α therapy were established. About 10% of the patients were randomly drawn as the test set. Responses to IFN-α therapy were divided into CR, partial response (PR) and non-response (NR). The mixed set of PR and NR was recorded as PR+NR.

RESULTS: Stratified by therapy duration, the most significant baseline predictive factors were alanine aminotransferase (ALT), HBV DNA level, aspartate aminotransferase (AST), HBV genotype, S, G, age and gender. According to the established model, the accuracies for sustained CR and PR+NR, respectively, were 86.4% and 93.0% for the training set, 81.5% and 91.0% for the test set. For the scoring system, the sensitivity and specificity were 78.8% and 80.6%, respectively. There were positive correlations between ALT and AST, and G and S, respectively.

CONCLUSION: With these models, practitioners may be able to propose individualized decisions that have an integrated foundation on both evidence-based medicine and personal characteristics.

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Key words: Chronic hepatitis B; Interferon-α; Patient selection; Predictive model; Scoring system; Treatment outcome

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INTRODUCTION

Chronic hepatitis B (CHB) is one of the most refractory diseases that mankind faces and is a serious global public health problem. Hepatitis B virus (HBV) infection often leads to acute or chronic hepatitis B, hepatocellular carcinoma (HCC) and other complications. Of approximately 350 million carriers of HBV worldwide, about 1 million die from chronic complications, such as cirrhosis, HCC or both every year. According to Liu et al, there is a 9% rate of HBV surface antigen (HBsAg) in the general population in China. In the United States, there are an estimated 1.25 million HBV carriers. Currently, available antiviral options can be divided into 2 types, interferon-α (IFN-α) and nucleoside/nucleotide analogues, including conventional IFN-α, pegylated IFN-α (PEG-IFN), lamivudine, adefovir dipivoxil, entecavir, telbivudine, etc. IFN-α is one of the major choices; however, some factors greatly hinder its wide range of applications. First of all, the expense of antiviral therapy is considerable in either underdeveloped or developing countries; in addition, there are several side effects, such as fatigue, flu-like syndrome and others; ultimately, the most important aspect is that only a proportion of patients may achieve a response after therapy. Thus, antiviral therapy is not generally accepted by patients.

Predicting the efficacy of IFN-α is crucial before attempting treatment for CHB patients. Some factors, such as HBV genotype A or B, lower viral load, higher serum alanine aminotransferase (ALT) levels, higher grading (G) of intrahepatic inflammation, and lower staging (S) of liver fibrosis, have been identified to be the predictors of the outcome of IFN-α therapy in HBV e antigen (HBeAg)-positive patients. Female gender, shorter course of disease, having mild liver fibrosis, having good compliance with therapy, absence of co-infection and an early virological response at the 12th wk also indicate a good therapeutic outcome. Sometimes, however, patients do not have all the “positive” predictors. They may also have one or more “negative” predictors. For example, a patient infected by HBV of genotype C, has a high viral load, accompanied by high ALT and high G. Is he suitable for IFN-α treatment? As pointed out by the European Association for the Study of the Liver, the HBV genotype has a poor individual predictive value, and currently, genotype alone should not define the choice of treatment. These types of issues may be challenging for both practitioners and patients. Owing to the trials that had rigorous designs, many patients have benefited from evidence-based medicine developed in the last several decades. However, evidence-based medicine aims at the resolution of issues which came from individuals with a common background whereas individual information is not always taken into account. The current research aims at making a sensible decision that has an integrated foundation in both evidence-based medicine and personal characteristics.

We therefore conducted the present study to determine (1) baseline predictive factors for the response to IFN-α; (2) what was the relationship between these predictive factors; (3) whether a predictive algorithm for IFN-α treatment of CHB can be derived from these factors; and (4) what was the efficacy of the model.

MATERIALS AND METHODS

Patients

During the period between July 2005 and November 2008, all HBeAg-positive CHB patients were followed up for their response to IFN-α if they initially started IFN-α treatment in our Liver Division, the 174th Hospital of the PLA, the Traditional Chinese Medicine Hospital of Xiamen, Zhongshan Hospital Xiamen University, Xiamen, or Macheng Hospital, Hubei. Patients were recruited according to the guidelines in China, and were administrated with 5 MU of conventional IFN-α every other day for 24 wk or longer. The patients’ baseline information was collected, including age, gender, blood tests, G, S, HBV DNA, genotype, etc. Several studies have indicated the potential benefits of extended duration of IFN-α or PEG-IFN therapy regarding a sustained response or suppression of chronic complications. Thus, duration was also recorded for balancing the effect of therapy span. Patients were excluded if they had HCC on presentation or other concomitant diseases including hepatitis A, C or D virus infection, autoimmune hepatitis, Wilson’s disease, primary biliary cirrhosis and alcoholic liver disease. Patients with the following conditions were also excluded: pregnancy, mental disorders (such as severe depression), uncontrolled epilepsy, alcohol abuse, narcotic abuse, uncontrolled autoimmune disorders, decompensated liver cirrhosis, symptomatic heart disease, neutrophil count below 1.0 × 109/L and/or platelet count below 50 × 109/L before treatment, had received or were receiving any other form of established treatment for CHB. Finally, 474 patients were included in the current study. For the treatment of HBeAg-positive CHB, a combined response (CR) was defined as ALT levels returning to normal, HBV DNA < 105 copies/mL, and/or seroconversion; partial response (PR) was defined as ALT levels returning to normal, HBV DNA < 106 copies/mL, but no seroconversion; whereas non-response (NR) refers to no CR or PR observations. The mixed set of PR and NR was recorded as PR+NR. A sustained response was defined as the response at the 24th wk after cessation of IFN-α treatment.

Monitoring of patients

Patients were followed up every 1-2 mo by monitoring HBsAg status, HBeAg/anti-HBe status, HBV DNA level,
ALT, aspartate aminotransferase (AST), α-fetoprotein (AFP), complete blood count and mental status. Complete blood counts were taken once every 1-2 wk for the first month, then once per month until cessation of treatment. Other tests, such as thyroid function, blood glucose, routine urinalysis, were taken once every 3 mo. For patients who had abnormal thyroid function at baseline, appropriate therapy was initiated, and thyroid function was closely monitored during antiviral therapy. If there was evidence of a depressive disorder or suicidal tendency, treatment was stopped and patients were closely monitored. Ultrasound of the liver was scheduled for patients with AFP levels greater than 20 ng/mL. Patients were suggested to stop IFN-α administration if CR or NR occurred after therapy for 24 wk, or if severe side effects developed during the course of treatment. Patients’ choices were also taken into account.

**Determination of HBV genotypes and HBV DNA levels**
Sera from patients on presentation were taken for the following tests: (1) HBV genotyping performed by the polymerase chain reaction (PCR)-fluorescence detection kit for HBV genotype B, C according to the manufacturer’s instructions (Bioselex, Hangzhou, China); and (2) HBV DNA levels were determined by quantitative fluorescence PCR on the ABI 7000 (Applied Biosystems), with a lower limit of detection of 1000 copies/mL. HBV DNA levels below the lower detection limit were regarded as negative for statistical calculations.

**Statistical analysis**
Statistical analyses were performed using version R 2.8.1 (a language and environment for statistical computing, Vienna, Austria, ISBN 3-900051-07-0, http://www.R-project.org). The inter-variable correlation was determined by the Spearman rank correlation coefficient. The Gini index based on random forest methodology was used to determine whether the identified variables were associated with therapy outcomes. In the present study, the response to IFN-α therapy (dependent variable) was ordinal data. If the independent variable was ordinal data (such as ALT, AST, G, S, etc), Kendall’s τ-b test was adopted to test the statistical significance between independent variable and dependent variable. For the nominal independent variable (gender, genotype, etc), the Pearson χ² test was used.

About 10% of patients were randomly selected as the test set, and the remaining patients were employed as the training set. The predictive model was constructed with a support vector machine (SVM) package for the R platform. Accuracies for CR and PR+NR in the training set and test set were calculated. The above process was repeated 300 times and mean accuracy was calculated. Performance of the constructed predictive algorithm was evaluated by the mean accuracies for CR and PR+NR for the training set and test set. The scoring system for sustained CR (SCR) was derived from our observations (Table 1) with computer-aided minor adjustment accord-

| Table 1 Baseline demographic and virological data of the study population |
|---------------------------------|-----------------|
| Factor                      | n (range)       |
| Sex (M:F)                    | 345:129         |
| Age (yr)                     | 29.8 (10-58)    |
| ALT (U/L)                    | 250 (16-1908)   |
| AST (U/L)                    | 146 (24-3304)   |
| Genotype (A:B:C)¹            | 51:212:211      |
| HBV DNA (log copies/mL)      | 7.35 (5.00-9.83) |
| Fibrosis staging, S (0:1:2:3:4)| 10:154:157:114:39 |
| Histology activity index, G (1:2:3:4) | 39:215:169:51 |

Continuous variables are expressed as median (range). B, C refers to genotype B, C, respectively; genotype B and C co-infection and other genotypes were named as A. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HBV: Hepatitis B virus.

**RESULTS**

**Demographics**
A total of 474 CHB patients were enrolled. The baseline demographics, liver function tests, liver biochemistry, histology data and virological data are listed in Table 1.

As shown in Table 2, the ratios of CR, PR and NR at the 24th wk after cessation of IFN-α therapy were 34.4%, 45.1% and 20.5%, respectively. It should be pointed out that genotype A in the current research refers to co-infection of genotype B and C, and other genotypes beside B and C.

**Patients’ factors and treatment factor for the response to IFN-α therapy**
As shown in Table 2, female patients had a higher chance of a CR compared to male patients (41.1% vs 31.9%, P < 0.001; Kendall’s τ-b test). Genotype B had a preferential effect on CR (45.3% and 25.1% for genotype B and genotype C, respectively, P < 0.001, Pearson χ² test). ALT and AST had a positive reciprocal relationship with treatment response (P < 0.001; Kendall’s τ-b test) (Table 2).
Table 2  Individual factors of patients with diverse responses at the 24th week after cease of interferon-\(\alpha\) therapy

| Variable          | CR    | PR    | NR    |
|-------------------|-------|-------|-------|
| Sex (M:F)         | 110:53| 163:51| 72:25 |
| Age [0-14):(15-24):(25-44):\(\geq 45\), yr] | 3:64:123:5 | 5:47:148:14 | 2:21:71:3 |
| ALT [1-5):2-3):3-5):5-10):\(\geq 10\), ULN] | 75:27:75:49 | 27:41:74:33 | 19:31:31:33 |
| AST [0-1):1-2):2-3):3-5):5-10):\(\geq 10\), ULN] | 1:22:30:49:13:18 | 12:76:53:24:10 | 9:50:18:14:6:0 |
| Genotype (A:B:C)  | 14:96:53 | 30:101:83 | 7:15:75 |
| HBV DNA [5-5.99):(6-6.99):(7-7.99):(8-8.99):(\(\geq 9\), log copies/mL] | 21:55:56:26:5 | 19:65:79:49:2 | 5:31:77:21:3 |
| Fibrosis staging, S (0:1:2:3:4) | 2:54:51:48:8 | 7:68:71:50:18 | 1:32:55:16:13 |
| Histology activity index, G (1:2:3:4) | 11:71:60:21 | 22:95:77:20 | 6:49:32:10 |
| Responses (CR:PR:NR) | 163 | 214 | 97 |

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ULN: Upper limit of normal; HBV: Hepatitis B virus; CR: Combined response; PR: Partial response; NR: No response.

Table 3  Inter-variable correlations determined by the Spearman rank correlation coefficient

| Variable          | Gender | Age | Grading | Staging | ALT | AST | DNA | Genotype | Duration | Y F6 m $^2$ |
|-------------------|--------|-----|---------|---------|-----|-----|-----|----------|----------|-------------|
| Gender            | 1.00   | 1.00|         |         |     |     |     |          |          |             |
| Age               | 0.06   | 1.00|         |         |     |     |     |          |          |             |
| Grading           | -0.11$^a$ | 0.05| 1.00    |         |     |     |     |          |          |             |
| Staging           | -0.06  | 0.08| 0.74$^b$| 1.00    |     |     |     |          |          |             |
| ALT               | 0.05   | -0.01| 0.13$^b$| 0.02    | 1.00|     |     |          |          |             |
| AST               | -0.13$^b$ | -0.04| 0.25$^b$| 0.17$^b$| 0.73$^b$| 1.00|     |          |          |             |
| DNA               | -0.09  | 0.04| -0.04   | -0.10$^b$| 0.07| 0.09$^b$| 1.00|          |          |             |
| Genotype          | 0.09$^a$ | 0.00| -0.01   | 0.01    | 0.09| 0.03| -0.12$^b$| 1.00    |          |             |
| Duration          | 0.05   | -0.03| -0.02   | 0.05    | 0.00| -0.04| 0.03| 0.02     | 1.00    |             |
| Y F6 m $^2$       | 0.05   | -0.01| -0.03   | 0.00    | -0.39$^b$| -0.35$^b$| 0.06| 0.25$^b$| -0.07    | 1.00       |

$^a$P < 0.05, $^b$P < 0.01, $^c$log copies/mL; $^d$Response after 6 mo of follow-up. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

Inter-variable correlations

The correlations between variables were determined by the Spearman rank correlation coefficient. As shown in Table 3, there were positive reciprocal relationships between G and S (0:1:2:3:4), ALT and AST (0.35, $P < 0.01$), AST and ALT (0.73, $P < 0.01$), Baseline ALT (0.39, $P < 0.01$), AST (0.35, $P < 0.01$) and genotype (0.25, $P < 0.01$) had a substantial predictive effect on the sustained response. The correlations between G and S, ALT and AST are illustrated in Figure 1A and B.

Multivariate analysis for factors associated with the response to IFN-\(\alpha\) therapy

Stratified by duration of IFN-\(\alpha\) therapy, Gini index analysis showed that baseline predictors, from highly significant to least significant, were ALT, HBV DNA in log copies/mL, AST, genotype, S, G, age and gender (Table 4).

Predictive algorithm for the SCR to IFN-\(\alpha\) therapy

Based on SVM, a predictive model was developed for the SCR to IFN-\(\alpha\) therapy. According to the established model, the accuracies for SCR and PR+NR respectively were 86.4% and 93.0% for the training set, 81.5% and 91.0% for the test set.

Predictive scoring system for the SCR to IFN-\(\alpha\) therapy

Based on our data provided in Table 2 with computer-aided minor adjustment according to other data, $^{[34,69]}$, a predictive scoring system was developed for the SCR to IFN-\(\alpha\) therapy. The odds ratio of SCR score was 15.25 (95% CI: 9.65-24.68, $P < 0.001$) indicating that the scoring system had an excellent prediction performance. By optimizing with the Youden’s index, the optimal cut-off for the prediction of SCR was 169. This cut-off had good sensitivity and specificity and had been accurately validated by the leave-one-out validation (Table 5). The AUCs were as high as 0.797 (95% CI: 0.773-0.812) for SCR prediction (Figure 2A). The odds ratio of SCR according to the scoring system is depicted in Figure 2B.

Table 4  Significance of baseline factors for sustained combined response to interferon-\(\alpha\) therapy

| Variable          | CR   | PR   | NR   | Mean decrease accuracy | Mean decrease Gini |
|-------------------|------|------|------|------------------------|-------------------|
| ALT               | 2.242| 0.860| 2.611| 1.363                  | 42.806            |
| Duration          | 0.536| 0.999| 0.251| 0.507                  | 36.340            |
| HBV DNA           | 0.603| 0.742| 0.015| 0.553                  | 35.713            |
| AST               | 1.045| -0.243| 0.955| 0.502                  | 35.488            |
| Genotype          | 1.101| 1.803| 3.095| 1.269                  | 30.462            |
| Staging           | 0.737| -0.058| -0.147| 0.205                  | 29.400            |
| Genotype          | -0.033| 0.030| -0.035| 1.01812               | 23.283            |
| Age               | -0.069| 0.094| 0.160| 0.050                  | 20.944            |
| Gender            | -0.125| 0.478| -0.084| 0.186                  | 14.396            |

CR: Combined response; PR: Partial response; NR: No response; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HBV: Hepatitis B virus.
**DISCUSSION**

In summary, the main findings and results of the current research include: (1) development of an accurate predictive model for the SCR to IFN-α therapy; (2) deduction of a scoring system for SCR as the data mining method may be unavailable to most the clinicians; (3) identification of positive reciprocal relationships between G and S, ALT and AST; (4) a predictive role of baseline ALT, AST and genotype for SCR; and (5) baseline predictive factors, listed from the greatest to the least significant, are ALT, HBV DNA, AST, genotype, S, G, age and gender.

The predictive factors for the response to IFN-α therapy have been extensively investigated; however, response prediction for individual patients remains uncertain. First, evidence-based medicine aims at a therapeutic strategy for patients with a similar background rather than a given patient. Additionally, a given individual may have “positive” predictive factors and “negative” predictive factors at the same time. Thus, patients or even clinicians may be perplexed by the probability estimation of therapy outcome. This leads to significant profligacy of health resources and a delay in treating patients who need an appropriate antiviral intervention. Fortunately, the present study may facilitate the management of these difficulties. One of the limitations of the current study is that most of the genotypes are B and C, or co-infection of B and C, which is in accordance with the report by Zeng et al\[16\]. There are not enough patients infected by other genotypes of HBV for statistical analysis. Another limitation is that treatment with conventional IFN-α rather than PEG-IFN was evaluated in the present research. Although PEG-IFN was extensively prescribed in developed countries, its application was greatly hindered by its high cost in developing countries. In China, there is great disparity in the prescription costs of IFN-α and PEG-IFN. We cannot recruit enough patients administrated with PEG-IFN for statistical analysis. However, IFN-α and PEG-IFN share the same bioactive molecule *in vitro* and similar baseline predictors\[16\]. Therefore, using our scoring system, which was easily employed in clinical practice, the response to PEG-IFN therapy may be predicted with reasonable accuracy. If statistical packages were available, higher predictive accuracy could be achieved.

In line with several studies\[12,17\], genotypes B or C have dramatically different effects on treatment response. Apart from genotypes, the present study also found that increasing HBV DNA levels were associated with a stepwise decrease in the response, which was similar to that of S; in contrast, increasing ALT, AST and G played an opposite role. Patients with higher ALT, AST and G tended to have better outcomes. According to the inter-variable correlation analysis, there were significantly positive reciprocal relationships between ALT and AST, G and S, respectively. The correlation between ALT and AST sounds reasonable, which may be a result of parallel release of intracellular contents after immune injury.
We developed a predictive model that was shown to have parallel accuracies for both a training set and test set by adjusting kernel parameters, which ensured that satisfactory sensitivity may be achieved for samples out of the observation pool. In other words, the established model would have a reasonable predictive accuracy for samples out of the optimal cut-off value of 169.

This score was validated by the stringent leave-one-out statistical analysis with high sensitivity and specificity of 78.2% and 79.9%, respectively, for the prediction of SCR. Using these SCR scores, the practitioner can calculate the prognosis of a patient on presentation, which is important for devising individual management of the patient. The practitioner can also identify very high-risk patients who should be recommended for treatment by nucleoside/nucleotide analogues to obtain good results.

In clinical practice, we are not aware of any predictive score for the SCR to IFN-α therapy in HBeAg-positive CHB patients with the integration of potential predictive factors. Our novel predictive algorithm and SCR score may serve as an excellent reference for clinicians to decide who should undergo IFN-α therapy. With these models, practitioners would be able to propose individualized treatment paradigms that have an integrated foundation in both evidence-based medicine and personal characteristics. It has extensive potential clinical use to identify CHB patients who have a high potential of a SCR to IFN-α therapy. These patients should be suggested to be treated by IFN-α to delay or prevent lethal complications of CHB such as liver cirrhosis and HCC.

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