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SHORT COMMUNICATION

Predictors of Histologic Severity in Chronic Hepatitis B-infected Patients☆

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The role of liver biopsy in chronic Hepatitis B treatment guidelines remains incompletely defined. Our aim was to correlate histologic disease severity with demographic, biochemical and virologic parameters as currently used in Hepatitis B treatment guidelines. We conducted an Institutional Review Board (IRB) approved retrospective cross-sectional study of chronic Hepatitis B patients between January 2001 and July 2009. Patients with at least two Alanine Aminotransferase (ALT) values (6 months apart), with detectable Hepatitis B DNA quantitative levels at the time of initial evaluation, unchanged HBeAg status over a minimum of 6 months but no prior history of antiviral therapy, alcohol abuse, co-infection, hepatocellular carcinoma, iron overload or liver decompensation were reviewed. Advanced histological disease was defined as a METAVIR score of greater than or equal to stage and/or grade 3 (≥S/G 3). Multivariable binary logistic regression was used to determine the independent predictors of advanced histology. One hundred and twenty-eight patients met inclusion criteria. On multivariate logistic regression analysis, viral load was not an independent predictor. However, age ≥40, abnormal ALT and HBeAg(+) were independent predictors of ≥S/G3. Controlling for ALT and HBeAg status, patients ≥40 years old had 14.5 times the adjusted odds of ≥S/G3 (95% CI, 4.24–49.54) while 31% of HBeAg(-) /Low Viral load patients had ≥S/G3. Current HBV-treatment guidelines do not fully predict advanced histological disease. In the group where all the current guidelines recommend observation without treatment, one third had advanced histology on liver biopsy.

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1. Introduction

The prevalence of chronic hepatitis B (CHB) is estimated to be 350 to 400 million patients.[1] At least 1.25 million cases are in the US.[2] In the US, most *de novo* Hepatitis B virus (HBV) infections occur in adolescence and early adulthood but in Asia most occur via vertical transmission. Despite an aggressive policy of vaccination and treatment, immigration from endemic areas of the world has contributed to this significant disease burden. It is estimated that 15–40% of patients will develop serious sequelae of advanced liver disease during their lifetime.[3,4] Timely and appropriate antiviral therapy is crucial to prevent complications, such as cirrhosis and hepatocellular carcinoma (HCC).[3] However, the appropriateness and timing of treatment remain incompletely defined.

Published CHB treatment guidelines[5–10] advocate treatment decisions based on the ALT, HBeAg, and viral load (VL) status. Age was recently added to the US guidelines as a relatively minor component. Presently, a liver biopsy is suggested for those who do not meet clear-cut criteria for treatment.[5] The accuracy of these criteria have been questioned as a significant number of patients with or at risk for advanced liver disease or HCC may be excluded from treatment consideration when the guidelines are applied.[9]

Little data exist linking treatment algorithms with histologic severity in HBV infected patients. It is possible that HBV infected patients with ALT values close to the upper limit of normal may have abnormal histology and are, therefore, at an increased risk of morbidity. With little supporting data, age of 40 has been added to some treatment guidelines to aid with treatment decisions.[5] However, a histologic evaluation with a liver biopsy remains the most accurate indicator of liver disease severity and, historically, it has been a fundamental tool to determine prognosis.[11]

The specific aim of our study was to assess how the demographic, biochemical, serological and virological parameters used in

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HBV-treatment algorithms reflect histological disease severity in CHB-infected patients.

2. Patients and methods

We conducted an IRB approved retrospective review of all HBV infected patients referred to our center between January 2001 and July 2009. HBV infected patients with at least two ALT values (6 months apart), with detectable HBV DNA quantitative levels at the time of initial evaluation, unchanged HBeAg status over a minimum of 6 months and also a liver biopsy within 2 years of the collection of serological data. At our center, it has been our practice to routinely biopsy all patients with HBV infection and detectable viremia. Patients co-infected with HIV, HDV or HCV, on immunosuppression, other underlying liver disorders, alcohol abuse, evidence of iron overload, HCC or prior antiviral therapy before biopsy were excluded from data analysis.

Demographic, biochemical (ALT), serological (HBeAg status), VL and histologic data were collected for analysis. Laboratory reference values were used to define abnormal ALT ($>1 \times$ ULN). Patients were classified based on VL and HBe Ag status. High Viral Load (HVL) was defined as HBV DNA level of $\geq$2000 IU/mL in HBeAg(−) patients or $\geq$20,000 IU/mL in HBeAg(+) patients. A Low Viral Load (LVL) was defined as HBV DNA level of <2000 IU/mL in HBeAg(-) patients or <20,000 IU/mL in HBeAg(+) patients. METAVIR scoring was used for histologic analysis. Grade (G) indicates the activity of necroinflammation and Stage (S) represents the fibrosis score. A necroinflammatory score of 3 (A3) or more and/or fibrosis score of 3 (F3) or more was defined as an advanced histological liver disease ($\geq$ S/G3). The liver biopsies were interpreted by multiple experienced liver pathologists at the time of the liver biopsy following the same standard reporting guidelines.

To simulate the existing CHB treatment algorithms, we classified our patients into four groups based on the HBeAg status and viral load levels. Group A: HBeAg(-) and LVL, Group B: HBeAg(-) and HVL, Group C: HBeAg(+) and LVL and Group D: HBeAg(+) and HVL.

3. Data analysis and statistics

Categorical variables were compared with χ^2 test and continuous variables with student's t test. All statistical significance was assessed at 95% confidence intervals. Multivariable binary logistic regression were used to determine the independent predictors of CHB patients being $\geq$S/G3 on liver biopsy with the area under the receiver operator characteristic curve (AROC) indicating the predictive accuracy of that model. The Pearson χ^2 tested the goodness of fit of the model. All statistical analysis was performed using the SPSS statistical software for windows Ver. 11.0 (SPSS, Chicago, IL, USA). $P < 0.05$ was considered significant.

4. Results

Seven hundred and seventy-nine patients had Chronic Hepatitis B infection. A total of 128 patients met the inclusion criteria. Table 1 shows demographic and clinical characteristics of these patients. The mean (±SD) age at presentation was 46.4 (±12.7) years and 66% of patients were 40 years of age or older. Over all, 77 (60.2%) patients were males and 70 (54.7%) patients were Asians. Twenty-five (19.5%) patients in the study group were Vietnamese in origin. Only 55 (43%) of patients had an abnormal ALT based on the laboratory reference value. Similarly, 54 (42.2%) patients had HVL and the rest 74 (57.8%) patients had a LVL. Of the total, 41 (32%) patients were HBeAg(+) at the time of presentation.

Table 2 shows the clinical, biochemical, and histological characteristics of the patients according to their HBeAg status. We found no difference in the rate of gender or race/ethnicity between HBeAg positive and negative patients. We also did not see a significant difference in the rate of abnormal ALT between the HBeAg groups. Our HBeAg(+) patients did tend to be younger than 40 years of age and to have HVL compared to the HBeAg(-) patients ($p < 0.01$).

Table 1 Demographic and clinical characteristics of study CHB patients

Variable	n (%)
Age ≥40	85 (66.4)
RACE	
Asian (Vietnamese)	25 (19.5)
Asian (Chinese)	10 (7.8)
Asian (Cambodian)	7 (5.5)
Asian (Other)	28 (21.9)
African Americans	28 (21.9)
Caucasians/White	16 (12.5)
Hispanics	4 (3.1)
Other	10 (7.8)
GENDER	
Male	77 (60.2)
Female	51 (39.8)
ALT	
Normal ALT	73 (57.0)
Abnormal ALT	55 (43.0)
VIRAL LOAD	
Low viral load (LVL)	74 (57.8)
High viral load (HVL)	54 (42.2)
HBeAg + Status	41 (32.0)
Biopsy Grade and Stage:	
≥grade 3	29 (22.6)
≥stage 3	41 (32.0)
Advanced Disease (≥S/G3)	50 (39.1)
Group	
A: HBeAg(-) and LVL	67 (52.3)
B: HBeAg(-) and HVL	20 (15.6)
C: HBeAg(+) and LVL	7 (5.5)
D: HBeAg(+) and HVL	34 (26.6)

High Viral Load (HVL): HBV DNA level of ≥ 2000 IU/mL in HBeAg(-) or ≥ 20,000 IU/mL in HBeAg(+).
Low Viral Load (LVL): HBV DNA level of < 2000 IU/mL in HBeAg(-) or < 20,000 IU/mL in HBeAg(+).

The presence of advanced liver disease histology was evaluated in all patients. Overall, 39% of patients had advanced liver histology ($\geq$ S/G3); 51% of HBeAg(+) patients and 33% of HBeAg(-) patients (Table 2). Twenty-six (20%) patients had cirrhosis at the time of presentation.

Demographic, biochemical and virologic variables were compared between histology groups (Table 3). Three variables, an abnormal ALT value, HBeAg(+) status and age ≥40 years were independently associated with the presence of advanced liver disease histology ($\geq$ S/G3). Patient age ≥40 years conferred greatest risk for advanced liver disease [Odds ratio (OR), 14.5; 95%

Table 2 Demographic and clinical characteristics of CHB patients by HBeAg status

Variable	HBeAg Negative [n (%)]	HBeAg Positive [n (%)]	p value
Male	54 (62.1)	23 (56.1)	0.325
Age ≥40	66 (75.9)	19 (46.3)	0.001
Asian	44 (50.6)	26 (63.4)	0.120
HVL	20 (23.0)	34 (82.9)	0.000
Abnormal ALT	37 (42.5)	18 (43.9)	0.517
Advanced Disease (≥ S/G3)	29 (33.3)	21 (51.2)	0.041

High Viral Load (HVL): HBV DNA level of ≥ 2000 IU/mL in HBeAg(-) or ≥ 20,000 IU/mL in HBeAg(+).
Low Viral Load (LVL): HBV DNA level of < 2000 IU/mL in HBeAg(-)or < 20,000 IU/mL in HBeAg(+).

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