Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications


**Background:** Identifying risk factors for the development of complications of chronic hepatitis B (CHB) is important for setting up treatment criteria.

**Aim:** To determine risk factors for the development of complications in Asian CHB patients.

**Patients and methods:** A total of 3233 Chinese CHB patients (mean follow up 46.8 months) were monitored for liver biochemistry, viral serology, hepatitis B virus (HBV) DNA levels, acute exacerbation, hepatitis B e antigen (HBeAg) seroconversion, and development of cirrhotic complications and hepatocellular carcinoma.

**Results:** Median age for HBeAg seroconversion and development of complications was 35 years and 57.2 years, respectively. Patients with alanine aminotransferase (ALT) levels of 0.5–1 times the upper limit of normal (ULN) and 1–2 × ULN had an increased risk for the development of complications compared with patients with ALT levels <0.5 × ULN (p<0.0001 for both), HBeAg/antibody to hepatitis B e antigen status, and number of episodes, duration, and peak ALT levels of acute exacerbations were not associated with an increased risk of complications. In patients with complications, 43.6% had HBV DNA levels less than 1.42 × 10⁵ copies/ml. Male sex, stigmata of chronic liver disease, old age, low albumin, and high α fetoprotein levels on presentation were independently associated with increased cumulative risk of complications. Male sex, presence of hepatitis symptoms, old age, low albumin level, and presence of complications on presentation were independently associated with shorter survival.

**Conclusion:** Prolonged low level viremia causing insidious and continual liver damage, as reflected by ALT levels of 0.5–2 × ULN, is the most likely pathway for the development of complications in Asian CHB patients.

**Chronic hepatitis B (CHB) virus infection affects more than 400 million people globally, of whom 75% are Asians.** Although there have been marked advances in the therapeutic options for CHB recently, indications for treatment remain controversial. Guidelines from the American Association for the Study of Liver Diseases, European Association of the Study of Liver, and Asian-Pacific Association of the Study of Liver suggest that treatment should only be given when there is persistent elevated alanine aminotransferase (ALT) levels >2 times normal and hepatitis B virus (HBV) DNA levels of >10⁵ copies/ml for both hepatitis B e antigen (HBeAg) positive and negative patients. However, no study has proved that patients with values below these arbitrarily defined cut off levels are at a lower risk for the development of cirrhosis related complications or HCC. In fact, a recent study by Kim et al in the general population of Korea found that there was already an increased risk of mortality from liver disease in patients with ALT levels in the upper range of normal. It is essential that more evidence for establishing treatment criteria should be sought, especially as more potent and safe therapeutic agents will be available in the near future.

The aim of the present large scale study was to examine the factors determining the development of cirrhosis related complications and survival in Asian CHB patients.

**PATIENTS AND METHODS**

All Chinese CHB patients who were followed up in the Hepatitis Clinic, Department of Medicine, Queen Mary Hospital, Hong Kong, during the period from January 1976 to December 2000 were recruited. A total of 346 patients who already had cirrhosis related complications including ascites, spontaneous bacterial peritonitis (SBP), oesophageal varices, encephalopathy, or HCC (collectively termed as “complications”) on presentation were excluded from the study. Patients with hepatitis C (n = 25) and hepatitis D (n = 10) coinfection, a history of significant alcohol consumption (n = 19), evidence of coexisting autoimmune hepatitis (n = 4), Wilson’s disease (n = 5), or primary biliary cirrhosis (n = 5) were also excluded. In addition, 494 patients who received interferon, lamivudine, or other investigational modalities for the treatment of CHB were excluded because these would not represent the natural history of the disease. The long term outcome of interferon treated patients has been analysed and published separately. All of the studies of interferon included patients with normal as well as elevated ALT levels. Their exclusion should not bias the outcome of our current analysis.

All patients were positive for hepatitis B surface antigen by micro-particle enzyme immunoassay (MEIA; Abbott Laboratories, Chicago, Illinois, USA) for at least six months. HBeAg and antibodies to HBeAg (anti-HBe) (ELISA; Abbott Laboratories), liver biochemistry, and α fetoprotein (AFP) were checked every 3–6 months. Continual clinical assessments, including the development of ascites, were carried out.

**Abbreviations:** CHB, chronic hepatitis B; HBV, hepatitis B virus; ALT, alanine aminotransferase; ULN, upper limit of normal; HCC, hepatocellular carcinoma; HBeAg, hepatitis B e antigen; SBP, spontaneous bacterial peritonitis; anti-HBe, antibody to hepatitis B e antigen; AFP, α fetoprotein; PCR, polymerase chain reaction
The Mann-Whitney U test was used for continuous variables. Differences in paired parameters were tested by the Wilcoxon signed ranks test. The Kaplan-Meier method using the log rank test was applied for calculation of the cumulative risk of development of complications and survival. The Cox hazard proportional model was used to test the associations between different variables and the development of complications and survival.

RESULTS
Demographics
A total of 3233 HBV patients were recruited. Demographic data on presentation are shown in Table 1. Median and mean duration of follow up were 29 (range 6–291) months and 46.9 (SD 46.6) months, respectively.

HBeAg seroconversion
Among 1274 patients positive for HBeAg on presentation, 512 patients (40.2%) had HBeAg seroconversion at subsequent follow up. Median age at HBeAg seroconversion was 35 years (range 3.6–77.4).

Development of complications
A total of 170 patients (5.3%) developed at least one complication. The number of patients developing each complication was as follows: ascites 96 (3.0%) with 30 patients (0.9%) also having SBP, oesophageal varices 59 (1.8%), encephalopathy 40 (1.2%), and HCC 95 (2.9%). Of the 59 patients with oesophageal varices, 15 had clinical bleeding; the rest were detected by endoscopy. The cumulative risk for the development of complications is shown in Figure 1. By the end of 10 years and 15 years of follow up, 8% and 12% of patients, respectively, had developed complications.

Table 2: Median age and hepatitis B e antigen/antibody to hepatitis B e antigen (HBeAg/anti-HBe) status at the time of development of complications of cirrhosis and hepatocellular carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Age [y] at the time of complications (median [range])</th>
<th>HBeAg/anti-HBe (% anti-HBe +ve)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>57.7 (29–78.1)</td>
<td>30/66 (68.8%)</td>
</tr>
<tr>
<td>SBP</td>
<td>60.0 (32.2–78.0)</td>
<td>7/23 (76.7%)</td>
</tr>
<tr>
<td>Oesophageal varices</td>
<td>54.3 (25.4–82.3)</td>
<td>14/45 (76.3%)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>58.5 (27.6–83.1)</td>
<td>14/26 (65%)</td>
</tr>
<tr>
<td>HCC</td>
<td>59 (24.8–82)</td>
<td>18/77 (81.1%)</td>
</tr>
<tr>
<td>All complications</td>
<td>57.2 (24.8–83.1)</td>
<td>45/125 (73.5%)</td>
</tr>
</tbody>
</table>

SBP, spontaneous bacterial peritonitis; HCC, hepatocellular carcinoma.
Factors associated with the development of complications

Demographics on presentation

Males had a higher cumulative risk for the development of complications than females (p<0.0001). Patients who developed complications, compared with patients without complications, were older (median age 55 years (range 19–82) v 38 years (range 1–85); p<0.0001), had a higher chance of the presence of stigmata of chronic liver disease (p<0.0001), and were more likely to present with hepatitis symptoms (p<0.0001).

Liver biochemistry and AFP

Patients who developed complications had significantly lower median albumin levels, higher median ALT levels, higher median bilirubin levels, and higher median AFP levels on presentation compared with patients without complications (table 3). However, median bilirubin and AFP levels for those who developed complications were still within normal limits.

To determine the risk for the development of complications with respect to ALT levels, patients were stratified into five groups according to ALT levels on presentation: <0.5×ULN (n = 714); 0.5–1×ULN (n = 1006); >1–2×ULN (n = 297); >2–6×ULN (n = 737); and >6×ULN (n = 2596). The cumulative risk for the development of complications was highest for patients with ALT levels of 1–2×ULN (fig 2). In addition, patients with ALT levels of 0.5–1×ULN already had a significantly increased risk of complications compared with patients with ALT levels <0.5×ULN. The risk of complications started to decrease for patients with ALT levels of 2–6×ULN and became very low for patients with ALT levels above 6×ULN.

The effect of ALT levels during follow up on the cumulative risk for the development of complications was also calculated for patients with at least three ALT readings. Patients were categorised by median ALT levels according to the same criteria adopted above. As there were only nine patients with median ALT levels more than 6×ULN, they were grouped with patients with ALT levels >2–6×ULN. Again, patients with ALT levels >1–2×ULN had the highest risk for the development of complications (p<0.0001 and p = 0.0027 compared with patients with ALT <0.5×ULN and patients with ALT levels 0.5–1×ULN, respectively). Patients with ALT levels of 0.5–1×ULN also had a higher risk for the development of complications compared with patients with

Table 3 Liver biochemistry on presentation of patients with and without complications of cirrhosis

<table>
<thead>
<tr>
<th>No of patients</th>
<th>ALT &lt;0.5 × ULN</th>
<th>ALT 0.5–1 × ULN</th>
<th>ALT &gt;1–2 × ULN</th>
<th>ALT &gt;2–6 × ULN</th>
<th>ALT &gt;6 × ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &lt;0.5 × ULN</td>
<td>-</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.039</td>
</tr>
<tr>
<td>ALT 0.5–1 × ULN</td>
<td>&lt;0.0001</td>
<td>-</td>
<td>0.0004</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ALT &gt;1–2 × ULN</td>
<td>&lt;0.0001</td>
<td>0.0004</td>
<td>NS</td>
<td>0.0006</td>
<td>NS</td>
</tr>
<tr>
<td>ALT &gt;2–6 × ULN</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td>NS</td>
<td>0.013</td>
<td>-</td>
</tr>
<tr>
<td>ALT &gt;6 × ULN</td>
<td>0.039</td>
<td>NS</td>
<td>0.0006</td>
<td>0.013</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are median (range).

ALT, alanine aminotransferase; AFP, α-fetoprotein.

Figure 2 Cumulative risk of development of complications stratified according to alanine aminotransferase (ALT) levels on presentation. The table depicts p values for comparisons between different groups of patients. ULN, upper limit of normal.

Figure 3 Cumulative risk of development of complications in patients with α-fetoprotein (AFP) levels >100 ng/ml and with AFP <100 ng/ml during acute exacerbation of hepatitis B virus infection.
ALT levels <0.5× ULN (p = 0.0071). There were no significant differences in the risk for development of complications when patients with ALT levels >2–6× ULN were compared with patients with ALT levels <0.5× ULN and those with ALT levels 0.5–1× ULN.

HBeAg status on presentation
There was no significant difference in the cumulative risk for the development of complications between HBeAg positive patients and anti-HBe positive patients (p = 0.12). This was also true when each type of complication was analysed separately.

Effect of exacerbation
The effect of exacerbation on the development of complications was analysed with respect to the number of episodes of exacerbation, duration of exacerbation, peak ALT levels, and peak AFP levels. The only significant risk factor was peak AFP levels of 100 ng/ml or more during or after an exacerbation (p = 0.0001 compared with patients with AFP level less than 100 ng/ml) (fig 3).

HBV DNA levels
HBV DNA levels were measured in 2332 patients. Of these, 112 had paired serum samples before and after HBeAg seroconversion. In addition, 525 HBeAg positive patients and 1695 anti-HBe positive patients had samples at the last follow up for HBV DNA assays. Details of HBV DNA levels measured by Digene Hybrid Capture assay are shown in table 4.

Median HBV DNA levels of the 1695 anti-HBe positive patients, as determined by the Cobas Amplicor HBV Monitor test, was 7250 copies/ml (range <200–1.7×10^6). Only 386 patients (22.8%) had undetectable HBV DNA levels. HBV DNA levels were <10^3, >10^3–10^4, >10^4–10^5, and >10^5 copies/ml in 183 (10.8%), 320 (18.9%), 259 (15.3%), and 547 (32.3%) patients, respectively.

HBV DNA levels were measured in 110 patients with complications: 21 patients before the complications developed (range 0.2–8.25 months); nine at the time of the complications; and 80 after the complications developed (range 0.41–193.5 months). Median HBV DNA level was 0.323×10^9 copies/ml (range <0.142–1700×10^9 copies/ml). Forty eight patients (43.6%) had HBV DNA levels undetectable by the Digene Hybrid Capture assay. The Cobas Amplicor HBV Monitor test was performed in 45 of these patients. Thirteen (28.9%) patients had undetectable HBV DNA (that is, <200 copies/ml). HBV DNA levels (copies/ml) of the remaining 32 patients were as follows: <10^3 in two patients (4.4%); >10^3–10^4 in 12 patients (26.7%); >10^4–10^5 in 10 patients (22.2%); and >10^5 in eight patients (17.8%).

Independent factors associated with development of complications and poor survival
Using the Cox proportional hazards model, male sex (p<0.0001), presence of stigmata of chronic liver disease (p = 0.045), increasing age (p<0.0001), low albumin level on presentation (p<0.0001), and high AFP level on presentation (p = 0.001) were found to be independent factors associated with a higher cumulative risk for the development of complications.

For survival analysis, male sex (p = 0.004), presence of hepatitis symptoms (p = 0.02), increasing age (p<0.0001), and low albumin level on presentation (p<0.0001) were found to be independent factors associated with a shorter actuarial survival.

DISCUSSION
The present study was limited by the relatively short period of follow up even though 307 patients (10.0%) were followed up for more than 10 years. Another limitation of the study was the absence of histological assessment. However, the end points of our study, the development of cirrhosis related complications and HCC, are of great clinical and prognostic relevance.

Several findings from the present study have direct implications for criteria for the treatment of CHB in the future. Firstly, the risk of complications increased as ALT levels on presentation increased from >0.5× ULN to 2× ULN. In contrast, patients with ALT levels above 6× ULN had a significantly lower risk for the development of complications (fig 2). These findings were confirmed using median ALT levels of patients during subsequent follow up. Acute exacerbations and high ALT levels (for example, >2× ULN) probably signify acute injuries to the liver which may not lead to permanent damage. This is probably analogous to the situation in acute viral hepatitis. However, in patients with only mild elevation of ALT, including those with ALT levels in the upper range of normal, the immune attack on the liver might be more insidious and chronic, leading eventually to more severe and permanent damage.

In the study of Kim et al showing an increased risk of mortality from liver disease in patients with ALT levels in the upper range of normal, it was suggested that the normal range of serum aminotransferase concentrations should be lowered in populations in which liver disease are common. Even though the authors did not test their subjects for hepatitis B or C markers, their findings confirm ours. The present guidelines for treatment suggest that only patients with ALT levels >2× ULN should be treated. This would exclude patients with the highest risks for the development of complications from treatment.

Secondly, in the Asian population, disease activity continues to progress in a proportion of patients after HBeAg seroconversion. Median age for the development of complications in our patients was 57.2 years (table 2). Median age of HBeAg seroconversion was 35 years. More than two thirds of the patients were already anti-HBe positive when they developed complications. The cumulative risk for the development of complications was comparable between patients positive for HBeAg and for anti-HBe on presentation. A Taiwan study by Yang et al. claimed that HBeAg positivity was associated with an increased risk of HCC. HBeAg status of patients and anti-HBe positive patients (p = 0.12). This was also true when each type of complication was analysed separately.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Hepatitis B virus (HBV) DNA levels of 2332 patients measured by Digene Hybrid Capture assay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>112 patients with paired serum</td>
</tr>
<tr>
<td></td>
<td>(n = 112)</td>
</tr>
<tr>
<td></td>
<td>HBeAg+ve phase (n = 525)</td>
</tr>
<tr>
<td>HBV DNA level (%)</td>
<td>27 (24.11)</td>
</tr>
<tr>
<td>HBV DNA level (×10^9 copies/ml)</td>
<td>4.15 (&lt;0.142–803.87)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>4.15 (&lt;0.142–803.87)</td>
</tr>
</tbody>
</table>

HBeAg, hepatitis B e antigen; anti-HBe, antibody to hepatitis B e antigen.

*p<0.001; †p<0.001
the patients in this study however was checked only at the
time of enrolment whereas the development of HCC was
observed during the subsequent 10 years of follow up.
HBeAg/anti-HBe status at the time of development of HCC
was not assessed. This study therefore can provide no clue as
to the HBeAg status of patients at the time of HCC
development. Another smaller Taiwan study found that
although HBeAg seroconversion confers a favourable out-
come in some patients, active hepatitis B may occur after HBeAg
seroconversion, leading to cirrhosis and HCC.13 McMahon et
al, in their study, found that “seroconversion from HBeAg to
anti-HBe, and even loss of hepatitis B surface antigen, did not
protect patients from development of hepatocellular carci-
noma”.14 These latter two studies confirm the findings of the
present study, that the majority of cirrhosis related complica-
tions and HCC develop after HBeAg seroconversion. The
onset of cirrhosis occurs during the prolonged process of
HBeAg seroconversion in Asian patients.15 Cirrhosis will con-
tinue to worsen or develop after HBeAg seroconversion.
Thus HBeAg seroconversion should only be regarded as a step
towards viral suppression, and therapy may need to be
continued after HBeAg seroconversion.
Thirdly, progression of cirrhosis is more likely to be related
to the low level of viraemia in a large proportion of patients
who are anti-HBe positive. In the current study, only 22.8% of
anti-HBe patients had undetectable HBV DNA levels by the
PCR based assay; 32.3% had more than 10^5 copies/ml. (That
the wild-type virus is as likely to cause complications as the
precore mutants have been analysed in a separate study.16)
Among the 56% of patients with complications in whom
HBV DNA levels were undetectable by the Digene Hybrid
Capture assay, over 70% had HBV DNA levels detectable by
the Amplicor HBV Monitor test. Twenty nine per cent of
patients had undetectable HBV DNA (that is, <200 copies/
ml). This is evidence against the proposal that disease
progression is unlikely once HBV DNA levels become less
than 10^5 copies/ml.17 Our findings support the conclusion of
Chu and colleagues18 that there is no cut off HBV DNA value
for differentiating active from inactive disease in HBeAg
negative patients. This implies that prolonged and maximal
suppression of HBV DNA to levels below the detection limit
of PCR based assays may be necessary to reduce the risk of
complications.
In conclusion, prolonged low level viraemia causing
insidious and continual liver damage, as reflected by
relatively mild elevations in ALT levels, is the most likely
pathway leading to the development of complications for
Asian patients with CHB. Long term antiviral therapy aiming
at maximal suppression of HBV even after HBeAg serocon-
version may be required for Asian patients.

Authors’ affiliations
M-F Yuen, H-J Yuan, D K-H Wong, J C-H Yuen, W-M Wong, A O-O
Chan, B C-Y Wong, K-C Lai, C-L Lai, Department of Medicine, The
University of Hong Kong, Queen Mary Hospital, Hong Kong

Conflict of interest: None declared.

REFERENCES
2 Lai CL. Chronic hepatitis B in Hong Kong: immunization strategies for the
control of hepatitis B virus infection. In: Zuckerman, eds. Hepatitis B in the
Asian-Pacific region vol. 1. Screening, diagnosis and control. London: Royal
3 Beasley RP, Hwang LY. Overview on the epidemiology of hepatocellular
carcinoma. In: Hollinger FB, Lemon SM, Margolis H, eds. Viral hepatitis and
4 Maddrey WC. Hepatitis B—an important public health issue. Clin Lab
5 Lok ASF, McMahon BJ. Chronic hepatitis B. Hepatology 2001;34:1225–41.
6 EASL Jury. EASL international consensus conference on hepatitis B. 13–14
September, 2002; Geneva, Switzerland. Consensus statement (long version).
management of chronic hepatitis B: An update. J Gastroenterol Hepatol
8 Kim HC, Nam CM, Jee SH, et al. Normal serum aminotransferase
concentration and risk of mortality from liver diseases: prospective cohort
9 Lai CL, Rasmawati M, Loo J, et al. Entecavir is superior to lamivudine in
reducing hepatitis B virus DNA in patients with chronic hepatitis B infection.
10 Lai CL, Leung NWY, Teo EK, et al. Results of a one-year international phase II
comparative trial of telbivudine, lamivudine, and the combination, in patients
with chronic hepatitis B. Hepatology 2003;38(supp1):72A.
therapy in Chinese patients with chronic hepatitis B infection: the effect on
HBeAg seroconversion and the development of cirrhosis-related
12 Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of
13 Hsu TS, Chien RN, Yeh CT, et al. Long-term outcome after spontaneous
HBeAg seroconversion in patients with chronic hepatitis B. Hepatology
14 McMahon BJ, Holck P, Bullkow L, et al. Serologic and clinical outcomes of
1,536 Alaska natives chronically infected with hepatitis B virus. Ann Intern Med
15 Edleston AL. The natural history of hepatitis B virus infection. Chemioterapia
16 Liaw YF, Tai DI, Chu CM, et al. The development of cirrhosis in patients with
17 Chen DS. Natural history of chronic hepatitis B virus infection: New light on an
18 Merican I, Guan R, Amarapuka D, et al. Chronic hepatitis B virus infection in
19 Yuen MF, Sablon E, Yuen HJ, et al. Relationship between the development of
precore and core promoter mutations and HBeAg seroconversion in chronic
20 Lok ASF, Heathcote EJ, Hoehnagle JH. Management of hepatitis B: 2000—
21 Chu CJ, Hussain M, Lok AS. Quantitative serum HBV DNA levels during
Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications


Gut 2005 54: 1610-1614 originally published online May 4, 2005
doi: 10.1136/gut.2005.065136

Updated information and services can be found at:
http://gut.bmj.com/content/54/11/1610

These include:

References
This article cites 18 articles, 2 of which you can access for free at:
http://gut.bmj.com/content/54/11/1610#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Hepatic cancer (474)
Hepatitis B (88)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/