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<td><strong>Author(s)</strong></td>
<td>Yuen, MF; Sablon, E; Hui, CK; Li, TM; Yuan, HJ; Wong, DKH; Doutreloigne, J; Bogaerts, V; Wong, BCY; Fan, ST; Lai, CL</td>
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Prognostic Factors in Severe Exacerbation of Chronic Hepatitis B

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Forty-seven patients with severe hepatitis B exacerbation were compared with patients who had mild exacerbation (n = 96) or no exacerbation (n = 96). Seventeen patients (36.2%) died or underwent liver transplantation. Preexisting cirrhosis and a prothrombin time (PT) of >30 s were associated with adverse outcome in 60.9% and 87.5% of patients, respectively. The rate of adverse outcome increased to 92.3% when albumin levels of <35 g/L and bilirubin levels of >200 μM were present. Other factors associated with adverse outcomes included peak bilirubin level, peak PT, time to reach peak PT, and the presence of encephalopathy and/or ascites. There was no difference in the frequency of precore mutations in patients with severe or mild exacerbation or without exacerbation. A significantly lower prevalence of core promoter mutants was found in patients with severe exacerbation (50%), compared with those who had mild exacerbation (81.3%; P = .004). Patients with severe exacerbation of hepatitis B with poor prognostic factors should be considered for early liver transplantation.

Chronic hepatitis B virus (HBV) infection is a disease of global importance that affects ~400 million people [1]. Exacerbation of chronic HBV infection occurs in ~40%–50% of hepatitis B e antigen (HBeAg)–positive patients and in 15%–30% of patients positive for antibodies against HBeAg (anti-HBe) [2–6]. Although these exacerbations are usually transient and asymptomatic, 1%–2.4% of patients later develop hepatic decompensation [3, 7, 8].

Patients with severe exacerbation pose a unique clinical challenge. Generally, they either experience spontaneous recovery with receipt of conservative treatment after prolonged hospitalization, or they die as a result of irreversible hepatic decompensation. The latter patients may benefit from early liver transplantation. To date, to our knowledge, there are no studies that have examined the prognostic factors for HBV-infected patients with severe exacerbation. Such prognostic factors could be important in determining which patients might benefit from early liver transplantation.

In addition, the role of precore and core promoter mutations in causing severe exacerbation is still controversial. Although some studies have suggested that precore mutations are associated with fatal exacerbation of chronic hepatitis B [9], the evidence remains inconclusive. Therefore, we sought to identify the prognostic factors for patients with severe exacerbation of chronic HBV infection and to examine the role of precore and core promoter mutations in such exacerbations.

PATIENTS AND METHODS

In this study, which was performed from 1 January 1998 through 31 December 2000, a total of 2542 patients with chronic hepatitis B were examined at the Hepatitis Clinic, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong, China. Eighty-nine patients with chronic hepatitis B were ad-
mitted to the hospital with symptomatic hepatitis. Of these patients, 47 had acute exacerbation of chronic HBV infection diagnosed and were recruited into the current study. All 47 patients had a sudden increase in the serum alanine aminotransferase (ALT) level from normal levels to more than twice the upper limit of normal. The other 42 patients were excluded from the study because they had the following concomitant conditions: 22 had acute hepatitis A or E, 5 were receiving antituberculosis treatment causing liver derangement, and 15 had alcoholic hepatitis. None of the patients had superimposed hepatitis C or D documented by the absence of the respective antibodies tested by Abbott Laboratories (Chicago, IL).

Because of the deranged clotting profiles in patients with severe exacerbation, liver biopsy was deemed unethical, and, therefore, liver biopsies were not performed. Cirrhosis was defined by ultrasonographic evidence of a small-sized and irregular liver, with or without splenomegaly, and/or a serum albumin level of ≤ 35 g/L recorded 3 months before the episode of acute exacerbation. All patients with cirrhosis were graded by the Child-Pugh score according to parameters obtained 3 months before the onset of acute exacerbation. Liver biochemistry values, including serum albumin, bilirubin, ALT, aspartate aminotransferase, alkaline phosphatase, α-fetoprotein, prothrombin time (PT), arterial ammonia (NH₃), urea, creatinine, and complete blood count, were determined at admission to the hospital. The liver biochemistry values, PT, and renal function were monitored daily after admission until the patient’s condition stabilized. Patients who died or who required liver transplantation were defined as having an adverse outcome. The hepatitis B serological markers were determined by EIA (Abbott Laboratories). Serum HBV DNA levels at admission were measured using the Digene Hybrid Capture II assay (Digene; lower limit of detection, 0.14 × 10⁶ copies/mL). For patients with HBV DNA levels that were undetectable by the Digene Hybrid Capture II assay, HBV DNA levels were further measured using the Cobas Amplicor HBV Monitor Test (Roche Diagnostics; lower limit of detection, 200 copies/mL) whenever adequate serum samples were available.

The presence of precore and core promoter mutations was tested by a research version of the line probe assay (INNO-LiPA HBV precore) which was developed by Innogenetics NV. The test contained specific probes covering the following motifs: (1) core promoter nt 1762/1764 wild type (A/G), (2) core promoter nt 1762/1764 mutant (A/A), (3) core promoter nt 1762/1764 mutant (A/T), (4) core promoter nt 1762/1764 mutant (T/A), (5) precore codon 28 (nt 1896) wild type (TGG), and (6) precore codon 28 (nt 1896) stop codon (TAG). The probes were applied on a nitrocellulose membrane, as described elsewhere [10]. In brief, HBV DNA was amplified for the core promoter/precore region by 5’ biotinylated PCR primers [11]. After reverse hybridization of the biotinylated PCR fragments in the LiPA format, streptavidin–alkaline phosphatase incubation and color development were used to identify reactive probes. The precore and core promoter mutations were tested in 24 patients (14 HBeAg-positive patients and 10 anti-HBe–positive patients). Of the other 23 patients, 14 had insufficient serum samples available and 9 had undetectable HBV PCR products, thereby precluding LiPA testing. The prevalence of precore and core promoter mutations in the 24 patients was compared with the prevalence in 2 control groups of HBV-infected patients from our Hepatitis Clinic, and control patients were matched with study patients by HBeAg and anti-HBe status at a ratio of 4:1. The first control group comprised 96 HBV-infected patients who had mild exacerbations (defined as an increase in serum ALT to more than twice the upper limit of normal, with the patients having no symptoms of hepatitis and no hepatic complications). The second control group comprised 96 HBV-infected patients with persistently normal ALT levels.

Presence of YMDD variant HBV was tested in the 2 patients who were receiving lamivudine before presentation by means of another line probe assay (INNO-LiPA HBV DR), which was developed by Innogenetics NV and which has been described elsewhere [12].

All statistical analyses were performed by SPSS for Windows, version 10.0 (SPSS). The Mann-Whitney U test was used for continuous variables with skewed distribution, and the χ² test with Yates’ correction or Fisher’s exact test was used for categorical variables. Logistic regression analyses were performed to test the associations between different variables and adverse outcome. Statistical significance was defined as P < 0.05.

RESULTS

Presenting features. The demographic data and clinical features at the time of presentation of the 47 patients are shown in table 1. Fifteen patients presented to our unit with acute exacerbation, and 32 developed exacerbation of HBV infection during follow-up at our Hepatitis Clinic.

HBV DNA and HBV virological markers. Fourteen (29.8%) of 47 patients had undetectable HBV DNA levels, as determined by the Digene Hybrid Capture II assay. Of these 14 patients, 10 had sufficient serum samples available for further testing with the Cobas Amplicor Monitor Test. Seven such patients had detectable HBV DNA levels (range, 208–6780 copies/mL), as determined with the more sensitive assay. Among the 23 HBeAg-positive patients, 3 (13.0%) had HBeAg seroconversion. Among 24 anti-HBe–positive patients, 1 (4.2%) had seroreversion to HBeAg.

Adverse outcome. Fifteen of the 47 patients died, and 2 patients underwent liver transplantation. The frequency of adverse outcome in patients with severe exacerbation of HBV infection was 36.2% (17 of 47 patients).
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prevalence of adverse outcomes between HBeAg-positive
and anti-HBe–positive patients (7 [30.4%] of 23 and 10
[41.7%] of 24, respectively). There were no significant differences in
the frequency of adverse outcomes between male and female patients
(15 [38.5%] of 39 and 2 [25%] of 8, respectively). Unfortunately, the number of female patients was too low for mean-
ingful statistical analysis. Patients with adverse outcomes had
a higher median age than did patients who survived with receipt of conservative treatment (median age, 43 years
[range, 35–68 years] vs. 36.5 years [range, 18–69 years], re-
spectively; \( P = .027 \)). There were no significant differences in
the frequency of adverse outcomes between HBeAg-positive
and anti-HBe–positive patients (7 [30.4%] of 23 and 10
[41.7%] of 24, respectively).

The differences in the initial laboratory findings between
patients who survived with receipt of conservative management
and patients with adverse outcome are shown in table 2. Pa-
tients with adverse outcomes had significantly lower median
albumin levels, higher median bilirubin levels, more prolonged
PTs, and lower platelet counts at admission to the hospital.

The frequency of adverse outcomes in patients with a PT of
\( >30 \) s at admission to the hospital was 85.7% (12 of 14 patients),
whereas, for patients who had a PT of \( \leq 30 \) s, the frequency
of adverse outcomes was only 15.2% (5 of 33) \( ( P < .0001 \) ). Of
the patients with initial albumin levels of \( >35 \) g/L and bilirubin
levels of \( \leq 200 \) \( \mu M \), none had adverse outcomes. By contrast,
the incidence of adverse outcomes was 49% (17 of 35) for
patients with albumin levels of \( \leq 35 \) g/L, and it was 63% (17
of 27) for those with bilirubin levels of \( >200 \) \( \mu M \) \( ( P = .001 
and \( P < .0001 \) ), respectively, compared with patients who had
no adverse outcomes).

A PT of \( >30 \) s was the single most important parameter for
poor prognosis. The sensitivity and specificity for predicting
adverse outcomes with a PT of \( >30 \) s at presentation were 0.71
and 0.93, respectively. The positive and negative predictive val-
ues were 0.86 and 0.85, respectively. Inclusion of the 2 other
adverse factors (i.e., albumin level of \( \leq 35 \) g/L and bilirubin
level of \( >200 \) \( \mu M \) ) increased the frequency of adverse outcomes
to 92.3% (12 of 13 patients). This was significantly higher when
compared with patients who did not have all 3 adverse factors
(5 [14.7%] of 34 patients; \( P < .0001 \) ). The sensitivity and spec-
ificity for predicting poor outcome by using a combination of
these 3 adverse factors were 0.71 and 0.97, respectively. The
positive and negative predictive values were 0.92 and 0.85,
respectively.

Preexisting cirrhosis and Child-Pugh score. The chance
of adverse outcome was higher for patients with cirrhosis than
for patients without cirrhosis (14 [60.9%] of 23 vs. 3 [12.5%]
of 24, respectively; OR, 12.4; 95% CI, 2.9–53.8; \( P < .0001 \) ). Of
the 23 patients with cirrhosis, only 2 had grade A cirrhosis,
according to the Child-Pugh score. They were grouped together
with 24 noncirrhotic patients in the following analysis. There
was an increasing chance of adverse outcome in patients with
a worsening Child-Pugh score (noncirrhosis or grade A, 4
[15.4%] of 26; vs. grade B, 5 [41.7%] of 12; vs. grade C, 8
[88.9%] of 9; \( P < .0001 \) ).

Sero logical and biochemical markers at admission to the
hospital. There were no significant differences in the fre-
cency of adverse outcomes between male and female patients
(15 [38.5%] of 39 and 2 [25%] of 8, respectively). Unfortunately, the number of female patients was too low for mean-
ingful statistical analysis. Patients with adverse outcomes had
a higher median age than did patients who survived with receipt of conservative treatment (median age, 43 years
[range, 35–68 years] vs. 36.5 years [range, 18–69 years], re-
spectively; \( P = .027 \) ). There were no significant differences in
the frequency of adverse outcomes between HBeAg-positive
and anti-HBe–positive patients (7 [30.4%] of 23 and 10
[41.7%] of 24, respectively).

Table 1. Demographic data for patients with severe exacer-
bation of chronic hepatitis B at admission.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tr>
<td>No. of patients</td>
<td>47</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>39 (18–69)</td>
</tr>
<tr>
<td>Ratio of men to women</td>
<td>39:8</td>
</tr>
<tr>
<td>Ratio of HBeAg-positive patients to anti-HBe–positive patients</td>
<td>23:24</td>
</tr>
<tr>
<td>Preexisting cirrhosis</td>
<td>23 (48.9%)</td>
</tr>
<tr>
<td>Child-Pugh grade</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>12</td>
</tr>
<tr>
<td>C</td>
<td>9</td>
</tr>
<tr>
<td>ALT level, median U/L (range)</td>
<td>615 (100–3840)</td>
</tr>
<tr>
<td>HBV DNA level, median copies×10^3/mL (range)</td>
<td>0.62 (&lt;0.14–1392)</td>
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</table>

Symptoms of hepatitis
| Total | 47 (100) |
| Jaundice | 40 (85.1) |
| Ascites | 13 (27.7) |
| Encephalopathy | 9 (19.1) |
| Variceal bleeding | 5 (10.6) |

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; Anti-HBe, antibodies against hepatitis B e antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.
a peak bilirubin level of >290 μM had adverse outcomes (P < .0001). There were no significant differences in peak ALT levels and the time to reach the peak ALT levels between patients who survived with receipt of conservative management and those who had adverse outcomes.

Development of encephalopathy and ascites. Patients who presented with encephalopathy at admission to the hospital had more adverse outcomes than did patients who did not have encephalopathy at admission (7 [77.8%] of 9 vs. 10 [26.3%] of 38; P = .007). Of the 38 patients in the latter category, 9 subsequently developed encephalopathy. These patients also had a significantly higher frequency of adverse outcome than did the remaining 29 patients who never developed encephalopathy (6 [66.7%] of 9 vs. 4 [13.8%] of 29; P = .005).

Thirteen patients presented with ascites at admission to the hospital, and the frequency of adverse outcome was significantly higher than the frequency among the 34 patients without ascites at admission (8 [61.5%] of 13 vs. 9 [26.5%] of 34; P = .041). The rate of adverse outcome was also significantly higher in the 4 patients who developed ascites after admission, compared with those who never developed ascites (3 [75%] of 4 vs. 6 [20%] of 30; P = .048). Patients who developed spontaneous bacterial peritonitis (3 patients) and those with variceal bleeding (5 patients presented with bleeding, and another 5 developed variceal bleeding after admission) did not have more adverse outcomes than did patients without these complications. However, this might be the result of the small number of patients affected.

Multivariate analyses of the factors associated with adverse outcome. By use of logistic regression analysis, the independent factors associated with adverse outcome for the parameters at admission included the following: preexisting cirrhosis (P = .001), high Child-Pugh score (P < .0001), low albumin level (P = .001), high bilirubin level (P < .0001), prolonged PT (P < .0001), and low platelet count (P = .015). For the subsequent monitoring, these factors were as follows: high peak bilirubin level (P < .0001), long peak PT (P < .0001), long duration to reach the peak PT (P = .021), development of encephalopathy (P < .0001), and presence of ascites (P = .003). There was also a trend for a longer time to reach peak bilirubin level to be an independent factor associated with adverse outcome (P = .053).

Lamivudine therapy. Two patients received lamivudine for 354 and 343 days before admission to the hospital with severe exacerbation. Both had YMDD to YVDD mutation and recovered with receipt of conservative management. Of the remaining 45 patients, 17 initiated lamivudine therapy during the exacerbation. The patients who received lamivudine had significantly poorer liver functions at admission than did those who did not receive lamivudine (respectively median albumin levels, 30 vs. 32.5 g/L [P = .044]; respective median bilirubin levels, 440 vs. 136 μM [P = .002]; and respective median PTs, 29.8 vs. 17.2 s [P = .01]). Ten (58.8%) of 17 patients who received lamivudine had an adverse outcome, whereas only 7 (25%) of 28 patients who did not receive lamivudine had an adverse outcome (P = .051). Poor outcome of the patients treated with lamivudine was not related to any delay in the initiation of lamivudine therapy. The median time between the onset of symptoms of exacerbation and the initiation of lamivudine therapy was 14 days (range, 0–62 days) for those who experienced adverse outcomes and 27 days (range, 2–56 days) for those who did not (P = .27).
**Significance of precore and core promoter mutations.** The demographic data and the prevalence of precore and core promoter mutations for the 24 patients with severe exacerbation, 96 patients with mild exacerbation, and 96 patients without exacerbation are listed in Table 3. There were no statistical differences between the 3 groups with regard to the median age, sex ratio, HBeAg/anti-HBe status, and HBV DNA level.

The precore and core promoter mutants, either alone or with the wild type, were present in 62.5% and 50% of the 24 patients with severe exacerbation, respectively. There were no significant differences in biochemical parameters, HBV DNA levels, and the incidence of adverse outcome in patients with or without either the precore or the core promoter mutants. There were also no significant differences in the prevalence of precore mutants between the 3 groups of patients. However, in HBeAg-positive patients, there was a significant trend for increasing prevalence of precore mutants in patients without exacerbation, with mild exacerbation, and with severe exacerbation (Table 3). This trend was not observed in anti-HBe–positive patients. The prevalence of core promoter mutations was significantly higher among patients with mild exacerbation than among patients with severe exacerbation ($P = .004$), although there was no difference when compared with patients who did not have exacerbation.

**DISCUSSION**

In this study, the mortality rate for severe exacerbation of chronic hepatitis B requiring hospitalization was 36.2%. Although older age at presentation was associated with higher mortality on univariate analysis, this factor was not shown to be significant on multivariate analysis. There was no difference in mortality between HBeAg-positive patients and anti-HBe–positive patients. Therefore, HBeAg status, and probably age, are not factors that should affect decisions regarding liver transplantation.

However, several important indicators of poor prognosis were identified. These included presence of cirrhosis, high Child-Pugh score, prolonged PT, high bilirubin level, low albumin level, and low platelet count at admission to the hospital. For patients with a PT of >30 s, the mortality rate was as high as 85.7%. For patients who also had an albumin level of ≤35 g/L and a bilirubin level of >200 μM, the mortality rate increased further to 92.3%.

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**Table 3. Demographic data and the prevalence of precore mutation and core promoter mutation among patients with hepatitis B who have different levels of exacerbation.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Level of exacerbation</th>
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<tr>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td>No. of patients</td>
<td>24</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>39.5 (25–69)</td>
</tr>
<tr>
<td>Ratio of men to women</td>
<td>20:4</td>
</tr>
<tr>
<td>Ratio of HBeAg-positive patients to anti-HBe–positive patients</td>
<td>14:10</td>
</tr>
<tr>
<td>ALT level, median U/L (range)</td>
<td>585 (100–2660)</td>
</tr>
<tr>
<td>HBV DNA level, median copies ×10^5/mL (range)</td>
<td>1.6 (&lt;0.14–1141)</td>
</tr>
</tbody>
</table>

**Precore region**

| Presence of WT only | 9 (37.5) | 44 (45.8) | 55 (55.2) |
| Presence of MT      | 15 (62.5) | 52 (54.2) | 43 (44.8) |
| Presence of MT only | 4 (16.7)  | 17 (17.7) | 13 (13.5) |
| Presence of WT and MT | 11 (45.8) | 35 (36.5) | 30 (31.3) |

**MT in HBeAg–positive patients, n/N (%)**

| MT in HBeAg–positive patients, n/N (%) | 9/14 (64.3) | 28/56 (50) | 17/56 (30.4) |

**MT in anti-HBe–positive patients, n/N (%)**

| MT in anti-HBe–positive patients, n/N (%) | 6/10 (60) | 24/40 (60) | 26/40 (65) |

**Core promoter region**

| Presence of WT only | 12 (50) | 18 (18.8) | 31 (32.3) |
| Presence of MT      | 12 (50) | 78 (81.3) | 65 (67.7) |
| Presence of MT only | 6 (25)  | 58 (60.4) | 44 (45.8) |

| Presence of WT and MT | 6 (25) | 20 (20.8) | 21 (21.9) |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; Anti-HBe, antibodies against hepatitis B e antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; MT, mutant; WT, wild-type.

*a* $P = .007$, by $χ^2$ test for trend.

*b* $P = .004$.

*c* $P = .000$.

*d* $P = .007$.  
*NS*
Serum ALT levels, both at admission and during subsequent monitoring, did not predict mortality. In addition, the virus load, as measured by HBV DNA levels at admission, was also of no prognostic value. As has been described elsewhere [13], patients frequently had undetectable or very low HBV DNA levels by the time they presented with symptoms. To ascertain whether the levels of HBV DNA are genuinely unrelated to the severity of the exacerbation, a well-designed study of the HBV DNA levels before or at the onset of exacerbation would be required.

Our study also identified additional risk factors during subsequent monitoring of the patients. These included the late increase in bilirubin levels to >290 μM, the late increase in the PT to >33 s, and the development of ascites and encephalopathy.

Lamivudine therapy, even when provided at a relatively early stage of exacerbation, was not linked to any survival benefit in cases of severe HBV exacerbation. However, patients who received lamivudine had very poor liver function at presentation. The degree of hepatic damage was probably too severe to be reversed by receipt of this nucleoside analogue.

We also found that the presence of precore and core promoter mutations did not affect the outcome for our patients. However, in HBeAg-positive patients, the prevalence of precore mutations was highest in patients with severe exacerbation (64.3%) (P = .007). It is quite possible that these patients exerted more-intense immunological pressure on wild-type HBV, thus favoring the emergence of precore mutants. Among anti-HBe–positive patients, there was no difference in the proportions of precore mutants among the patients with severe or mild exacerbation or without exacerbation. This finding is in accord with the findings of Loriot et al. [14], who reported that exacerbation is not related to precore mutations.

Core promoter mutants were found to occur in 81.3% of patients with moderate exacerbation, a significantly higher prevalence than that in patients with severe exacerbation (50%; P = .004). In vivo studies show that the presence of core promoter mutations is associated with lower virus loads, lower HBeAg levels, and lower DNA polymerase levels [15, 16]. It is conceivable that the reduced production of HBeAg might give rise to less intense immune-mediated damage.

In conclusion, several risk factors at presentation and during subsequent monitoring have been identified as indicators of poor prognosis for exacerbation of HBV infection. These factors could be useful in deciding whether early liver transplantation is warranted.

Acknowledgments

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References