Quantitative hepatitis B core antibody level may help predict treatment response in chronic hepatitis B patients

We read with interest the recent article by Dandri emphasising the use of novel quantitative biomarkers as tools for predicting treatment response and disease progression in chronic hepatitis B infection (CHB).[1] The authors carried out a comprehensive review of the clinical implications of quantitative measurement of viral biomarkers both in blood and in liver, such as: serum HBsAg, serum HBeAg and intrahepatic cccDNA, based on current knowledge.[1] In addition to these, we would like to propose a new potential prognostic biomarker in CHB: the quantitative hepatitis B core antibody (anti-HBc) level which may help predict treatment response in CHB patients.

Anti-HBc is one of most classical serological markers for HBV infection.[2] However, the clinical significance of quantitative anti-HBc level is still largely unknown. By using a newly developed double-sandwich anti-HBc immunoassay validated by the WHO anti-HBc standards,[3 4] we investigated its value in CHB patients.

In a cross-sectional cohort, we analysed the anti-HBc levels of 488 CHB patients and 350 healthy individuals with past HBV infection. The geometric mean level of anti-HBc in CHB patients was >1000-fold higher than that in individuals with past HBV infection ($p<0.001$, figure 1A). Among CHB patients, the anti-HBc levels in those who had elevated ALT levels (n=180) was significantly higher than those who had normal ALT levels (n=308) ($p<0.001$, figure 1A). Because elevated ALT levels in CHB is assumed to be due to a T-cell-

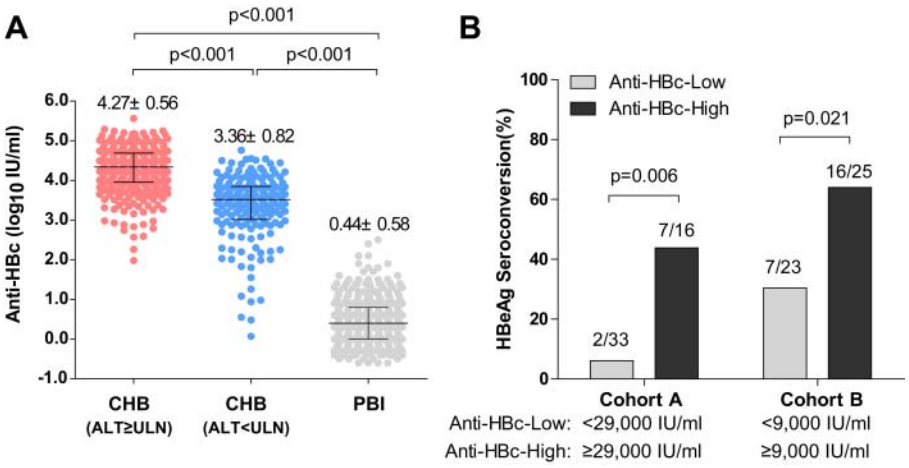

Figure 1 The quantitative anti-HBc levels in patients experiencing HBV infection. (A) Distribution of the serum anti-HBc levels during different phases of HBV infection. (B) The probability of seroconversion based on the baseline anti-HBc level grouping (high or low) according to the ROC-determined cut-off in patients receiving adefovir dipivoxil (Cohort A, 29 000 IU/ml) and peginterferon (Cohort B, 9000 IU/ml). PBI, past HBV infection; ULN, the upper normal limit.

mediated hepatocytolysis,[5] the parallel increasing anti-HBc levels may reflect the host-adaptive anti-HBV immune activity. Moreover, the quantitative anti-HBc, thus, might also predict the response of patients receiving anti-HBV therapies.

To test this hypothesis, we further retrospectively investigated the usefulness of the baseline anti-HBc levels in predicting post-treatment response in two cohorts (A and B). Cohort A consisted of 49 HBeAg-positive patients treated with adefovir dipivoxil at 10 mg/day for 96 weeks and followed by a 12-week observation between years 2004–2007. Cohort B included 48 HBeAg-positive patients receiving peginterferon α-2a (180 μg/week) for 24 weeks, and followed by a 24-week observation in years 2005–2009 (Cohort B). As shown in table 1, patients with and without HBeAg seroconversion (SR) at the end of follow-up in the two cohorts had comparable (p>0.05) baseline values for age, gender, the levels of ALT (or stratification by 5×ULN), HBV DNA, HBsAg and anti-HBc-IgM. However, the SR (+) patients had a significantly higher baseline anti-HBc levels than SR(–) patients, either in cohort A (p=0.005) or B (p=0.011). The predictive value (indicated by area under the curve for SR of the baseline anti-HBc level was 0.810 (95% CI 0.675 to 0.948, p=0.004) and 0.710 (95% CI 0.564 to 0.855, p=0.013) in cohorts A and B, respectively. Figure 1B showed the SR rate among patient groups classified by baseline anti-HBc level using the optimal cut-off indicated by the inflection point of the receiver operating characteristic in both cohorts. Patients with high baseline anti-HBc levels (≥29 000 IU/ml for cohort A or ≥9000 IU/ml for cohort B) had a higher SR rate than those with lower baseline anti-HBc levels (RR=7.22, 95% CI 1.69 to 30.9, p=0.006 in Cohort A; RR=2.10, 95% CI 1.06 to 4.17, p=0.021 in Cohort B). These results suggested that the pre-treatment anti-HBc level may be an additional predictor for post-treatment SR both in interferon or nucleos(t)ide analogue therapy.

In summary, baseline anti-HBc levels may serve as a useful marker indicating an ongoing host-immune activity against HBV, and the new findings may have clinical implications warranting further investigation.

Table 1 Analyses of baseline characteristics predicting HBeAg seroconversion (SR) in patients receiving adefovir dipivoxil (cohort A) and peginterferon (cohort B) treatments

	Cohort A			Cohort B		
Characteristics	SR(+)	SR(–)	p Value	SR(+)	SR(–)	p Value
No.	9	40	–	23	25	–
Age, yrs	35±4	36±6	0.87	34±11	36±10	0.54
Gender, males/females	7/2	37/3	0.45	17/6	18/7	0.88
Genotype, B/C	2/7	9/31	0.99	15/8	14/11	0.52
ALT, >5×/≤5× ULN	3/6	9/31	0.77	8/15	8/17	0.84
ALT, U/L	170±88	137±79	0.28	198±129	213±149	0.71
HBV DNA, $\log_{10}$ copies/ml	7.03±1.40	7.65±1.13	0.16	7.64±0.92	7.04±1.61	0.12
HBsAg, $\log_{10}$ IU/ml	4.32±0.16	4.39±0.65	0.78	4.01±0.42	3.92±1.07	0.70
Anti-HBc-IgM, S/CO value	3.13±1.39	2.51±2.49	0.47	3.38±2.85	2.72±3.43	0.47
Anti-HBc, $\log_{10}$ IU/ml	4.58±0.28	4.15±0.42	0.005	4.32±0.66	3.81±0.68	0.011

Data of Age, ALT activity, HBV DNA, HBsAg titier, IgM anti-HBc and anti-HBc level are expressed at Mean±SD; SR, HBeAg seroconversion.

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REFERENCES

1. **Dandri M,** Locarnini S. New insight in the pathobiology of hepatitis B virus infection. *Gut* 2012;**61**(Suppl 1):i6–17.
2. **Liaw YF,** Chu CM. Hepatitis B virus infection. *Lancet* 2009;**373**:582–92.
3. **Li A,** Yuan Q, Huang Z, *et al*. Novel double-antigen sandwich immunoassay for human hepatitis B core antibody. *Clin Vaccine Immunol* 2010;**17**:464–9.
4. **NIBSC.** *WHO International Standard: First International Standard for anti-Hepatitis B core antigen*. 2008. www.nibsc.ac.uk/documents/fu/95-522.pdf
5. **Maini MK,** Boni C, Lee CK, *et al*. The role of virus-specific CD8(+) cells in liver damage and viral control during persistent hepatitis B virus infection. *J Exp Med* 2000;**191**:1269–80.

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