CORRESPONDENCE

To the Editor:

We would like to point out an omission in the AASLD Practice Guidelines on Chronic Hepatitis B published in the February 2007 issue of HEPATOLOGY.[1] In the section discussing the counseling and prevention of hepatitis B on pages 508-509 and in the accompanying table (Table 3), when discussing infants born to hepatitis B virus (HBV)-infected mothers, the authors neglected to discuss the issue of breast-feeding. This is certainly worth mentioning because some mothers feel breast-feeding to be an integral part of the care they provide to their infants, and mothers prohibited from breast-feeding may feel some sense of inadequacy. As you know, breast-feeding is not prohibited in HBV-infected mothers, as proven by several studies, some of which are listed here.[2-4] Furthermore, because infants should routinely receive HBV immune globulin and HBV vaccine, they are almost universally protected against postpartum maternal HBV transmission.

We think an additional 1-2 sentences should be included in the guidelines to address this issue.

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References

1. Lok ASF, McMahon BJ. AASLD practice guidelines: chronic hepatitis B. HEPATOLOGY 2007;45:507-539.
2. American Academy of Pediatrics. Hepatitis B virus. In: Pickering LK, Baker CJ, Long SS, McMillan JA, editors. Red Book 2006: Report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL. American Academy of Pediatrics;2006:335-355.
3. Beasley RP, Stevens CE, Shiao IS, Meng HC. Evidence against breast-feeding as a mechanism for vertical transmission of hepatitis B. Lancet 1975;2:740-741.
4. Hill JB, Sheffield JS, Kim MJ, Alexander JM, Sercely B, Wendel GD. Risk of hepatitis B transmission in breast-fed infants of chronic hepatitis B carriers. Obstet Gynecol 2002;99:1049-1052.

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Reply:

We agree with Dr. Jhaveri and Dr. Murray that available data show that there is no evidence of hepatitis B transmission from infected mothers to infants who are breast-fed and that breast-feeding should not be prohibited, particularly for infants who receive appropriate prophylaxis with hepatitis B immune globulin and hepatitis B vaccine. Because of space constraints, it was not possible for the guidelines to include all aspects of hepatitis B management. We appreciate Dr. Jhaveri and Dr. Murray for bringing this to our readers' attention.

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External Validation of FibroIndex

To the Editor:

We read with interest the Koda et al. report on the description of a new panel of biomarkers for predicting significant fibrosis in patients with chronic hepatitis C (CHC) called FibroIndex.[1] This panel was derived from the platelet count, AST, and gamma globulin measurements. They built and validated their model on a cohort of 360 CHC patients with an estimation set (n = 240) and validation set (n = 120). The areas under the receiver operating characteristic (ROC) curves of FibroIndex for predicting significant fibrosis were 0.83 and 0.82 for the validation set, better than those of the Forns index and the aminotransferase-to-platelet ratio index (APRI). The ultimate utility of any noninvasive model for prediction of hepatic fibrosis depends on its practicality and validation by other investigators in a wide range of patients.[2] We studied the diagnostic accuracy of the FibroIndex and compared it to APRI, Forns index, and Fibrotest in a cohort of 125 CHC patients prospectively enrolled in Fibroscore, a French national multicenter study. Of the 125, 85 (68%) were men, and mean age was 47 ± 9 years. Signed informed consent was obtained from all patients before their inclusion. Liver biopsy and biochemical markers were done the same day. Liver biopsy was performed in each center and analyzed by the resident pathologist. For all patients, ultrasound examination was performed before liver biopsy. Information relating to the patient demographic data, risk factors, virological status, clinical examinations, biological data (platelets, prothrombin time ratio, serum albumin level) was prospectively recorded in each center on the day of biopsy. All data were anonymously recorded in the database. Diagnostic accuracies were measured using area under ROC curves (AUCs), sensitivities, specificities, and positive and negative predictive values. The Hanley-McNeil test[3] was used to compare AUCs; χ^2 or Fisher exact test were used to compare proportions. Serum samples were taken, on the day of biopsy, for determination of biochemical markers to assess FibroIndex, APRI, Forns index, and Fibrotest. Biochemical marker analysis was performed in accredited laboratories following the guidelines recommended for Fibrotest assessment by the authors of the initial publication.[4]

In the hospital-based cohort, gamma glutamyl transpeptidase and total bilirubin levels were measured using a Hitachi 917 Analyzer and Roche Diagnostics reagents (both from Mannheim, Germany). Alpha2-macroglobulin, apolipoprotein A1, and haptoglobin were measured using a Modular analyzer (BNII, Dade Behring; Marburg, Germany). Platelets were measured with a Beckman Coulter LH 750 hematology analyzer. Biochemical assays were performed on fresh serum, decanted, and stored for 72 hours maximum at 2°C/8°C while

Table 1. AUC Results

	F01 vs. F234 AUC(95% CI)		F01 vs. F34 AUC(95% CI)		F01 vs. F23 AUC(95% CI)		F012 vs. F3 AUC(95% CI)	
Test	Fibroscore	Koda et al.	Fibroscore	Koda et al.	Fibroscore	Koda et al.	Fibroscore	Koda et al.
FibroIndex	0.76 (0.68-0.83)	0.86 (0.81-0.92)	0.72 (0.64-0.80)	0.85 (0.79-0.91)	0.72 (0.63-0.80)	0.83 (0.75-0.90)	0.62 (0.53-0.72)	0.81 (0.73-0.89)
FT	0.78 (0.70-0.85)	–	0.80 (0.72-0.87)	–	0.74 (0.64-0.82)	–	0.73 (0.63-0.81)	–
APRI	0.81 (0.73-0.82)	0.82 (0.76-0.89)	0.78 (0.69-0.85)	0.81 (0.74-0.88)	0.77 (0.68-0.84)	0.78 (0.69-0.86)	0.71 (0.61-0.79)	0.77 (0.69-0.86)
Forns	0.80 (0.72-0.86)	0.84 (0.77-0.90)	0.78 (0.70-0.85)	0.83 (0.77-0.89)	0.76 (0.67-0.84)	0.78 (0.70-0.86)	0.73 (0.64-0.81)	0.76 (0.68-0.85)

protected from light. Cholesterol was measured on a Beckman Coulter Synchron CX 7 analyzer (Beckman Coulter France SA, Roissy, France). The assays of the specific proteins (alpha2-macroglobulin, haptoglobin, and apolipoprotein A1) were carried out on serum stored at 2°C/8°C for 5 days.

According to Metavir fibrosis staging, 6 of 125 (5%) patients were F0, 39 of 125 (31%) were F1, 36 of 125 (29%) were F2, 25 of 125 (21%) were F3, and 18 of 125 (14%) were F4. Note that the fibrosis distribution of our cohort is comparable to the one of the validation set of Koda et al.

The AUC results are presented in Table 1. For significant fibrosis, the AUC found in our cohort was lower than the one reported by Koda et al. (0.76 versus 0.86, *P* not significant). Our results observed for APRI and Forns index are similar to the corresponding results reported.

The distribution of our population cannot explain the discordance observed in the diagnostic accuracy. Among the 3 variables included in the FibroIndex (AST, platelet count, and serum gamma globulin), only the 2 former can be assessed with precision. Despite the fact that serum gamma globulin was higher in patients with scores of F2 or F3 than in those with scores of F0 or F1,[4] this parameter cannot be correctly assessed by electrophoresis. Gel electrophoresis is especially useful as an analytical method. Its advantage is that proteins can be visualized as well as separated, permitting a researcher to estimate quickly the number of proteins in a mixture or the degree of purity of a particular protein preparation.[5] Electrophoresis provided only a semiquantitative assessment of serum gamma globulin. Calculation was done by the formula: (% of the area under the pic) × (concentration of total proteins). This calculation gives only an estimation of the serum gamma globulin with expected fluctuations.[5] In our study, the same method that Koda et al. used was done to assess the serum gamma globulin.

In conclusion, robustness of the analysis should be assessed before a validation in clinical scores. The FibroIndex does not constitute for us a practical index for predicting significant fibrosis in patients with CHC. Moreover, FibroIndex has lower diagnostic accuracies than APRI, Forns index, or Fibrotest.

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References

1. Koda M, Matunaga Y, Kawakami M, Kishimoto Y, Suou T, Murawaki Y. Fibroindex, a practical index for predicting significant fibrosis in patients with chronic hepatitis C. HEPATOLOGY 2007;45:297-306.
2. Halfon P, Bourliere M, Deydier R, Botta-Fridlund D, Renou C, Tran A, et al. Independent prospective multicenter validation of biochemical markers (fibrotest-actitest) for the prediction of liver fibrosis and activity in patients with chronic hepatitis C: the fibropaca study. Am J Gastroenterol 2006; 101:547-555.
3. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839-843.
4. Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet 2001;357:1069-1075.
5. Fink PC. A fully automated serum electrophoresis system. J Clin Chem Clin Biochem 1981;19:379-386.

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Reply:

We are delighted that Halfon et al. provided external validation for FibroIndex. They proposed a problem in gamma globulin for the discrepancy between our study and their data. The importance of serum gamma globulin in chronic hepatitis C has already been reported by several investigators.[1-3] Imbert-Bismut et al.[1] reported that serum gamma globulin was higher in patients with F2 or F3 than in those with F0 or F1. Our other study series[3] also revealed that serum gamma globulin values were quantitatively correlated with staging scores. Therefore, it leaves no doubt that serum gamma globulin reflects the hepatic fibrosis in chronic hepatitis C.

Next, they point out that the measurement method of gamma globulin is not always reliable. We also emphasized the importance of the accuracy control of each parameter in the index comprising laboratory tests. In fact, we have described in the text that each parameter is under strict quality control. In our study, gamma globulin was measured using a single and dedicated analyzer with minimal interlaboratory variability (coefficient of variation at least $<6\%$) as well as aspartate aminotransferase (AST) and platelet count. Although Halfon et al. do not show their quality control of gamma globulin measurement, this discrepancy may indicate the importance of the standardization and the strict quality control of each parameter. Indeed, AUROCs of APRI and Forns index conducted by AST and platelet in our study are higher than those in Halfon's study.