Discordance between Liver Biopsy and FibroTest in Assessing Liver Fibrosis in Chronic Hepatitis B

Mi Sung Park¹, Beom Kyung Kim¹,²,³,⁴, Jae Yoeun Cheong⁴, Dong Joon Kim⁵, Jun Yong Park¹,²,³, Do Young Kim¹,²,³, Sang Hoon Ahn¹,²,³,⁶, Kwang-Hyub Han¹,²,³,⁷, Chae Yoon Chon¹,²,³, Seung Up Kim¹,²,³*

¹ Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea, ² Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea, ³ Liver Cirrhosis Clinical Research Center, Seoul, Korea, ⁴ Department of Gastroenterology, Ajou University School of Medicine, Suwon, Korea, ⁵ Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, Korea, ⁶ Brain Korea 21 Project for Medical Science, Seoul, Korea

Abstract

Background and Aims: The FibroTest (FT) demonstrated excellent diagnostic performance in the prediction of liver fibrosis in patients with chronic hepatitis B (CHB). Here, we aimed to identify predictors of discordance between FT and liver biopsy (LB) in Asian patients with CHB.

Methods: Consecutive patients with CHB who underwent both LB and FT on the same day between 2007 and 2010 were recruited from three medical institutes. Laboratory evaluations including specific parameters for calculating FT score, such as α2-macroglobulin, apolipoprotein A1, haptoglobin, γ-glutamyl transpeptidase, and total bilirubin levels, were obtained. The Batts and Ludwig scoring system was used for histological analysis.

Results: A total of 330 patients (200 male and 130 female) were analyzed. Discordances of at least two fibrosis stages between FT and LB were observed in 30 (9.1%) patients; using FT, fibrosis was underestimated in 25 patients and overestimated in 5 patients with reference to LB. Patients with discordance had a higher proportion of F3–4 (P<0.001) and F4 (P=0.012) compared with those with nondiscordance. The discordance rate was significantly higher in those with F3–4 than those with F1–2 (15.4% vs. 3.0%, P<0.001). Multivariate analysis demonstrated F3–4 at LB as the only independent factor for discordance (P<0.001; odds ratio 5.95). After adjusting fibrosis stages, neither necroinflammatory activity on histology nor serum ALT level influenced FT values independently.

Conclusion: Advanced fibrosis stage (F3–4) is the sole factor of discordance between FT and LB in Asian patients with CHB.

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Liver Biopsy Examination

Percutaneous LB was performed using a 16G disposable needle. The LB specimens were fixed in formalin and embedded in paraffin. Sections 4 mm thick were then stained with hematoxylin and eosin and Masson’s trichrome. All liver tissue samples were evaluated by an experienced hepatopathologist in each institute blinded to the patients’ clinical histories. Specimens that were shorter than 17 mm and considered by the pathologists to be unsuitable for fibrosis assessment were excluded from the analysis. Liver histology was evaluated semiquantitatively according to the Batts and Ludwig scoring system [14]. Fibrosis was staged on a 0–4 scale: F0, no fibrosis; F1, portal fibrosis; F2, periregional fibrosis; F3, septal fibrosis; and F4, cirrhosis. Significant fibrosis was defined as F2 or more, advanced fibrosis as F3 or more, and cirrhosis as F4.

Statistical Analysis

Continuous variables of patients with discordance and those without were compared with independent t-tests or Mann-Whitney U tests, as appropriate. The chi-squared or Fisher’s exact tests were used for categorical variables. Based on previous studies [15–17], discordance was defined as a discordance of at least two stages between fibrosis stages determined by the FT and LB. Subsequent multivariate analysis using binary logistic regression analyses was performed to identify independent factors related to discordance between fibrosis stage of the FT and LB. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were also indicated. Statistical analyses were performed using the SPSS software (ver. 18.0; SPSS Inc., Chicago, IL, USA). In all analyses, a value of P<0.05 was taken to indicate statistical significance.

Results

Baseline Characteristics of the Study Population

A total of 628 consecutive patients were screened for possible inclusion in the study. Based on the above exclusion criteria, a total of 330 patients (200 male and 130 female) were finally analyzed (Figure 1).

Liver Histology and Corresponding FT Values

The median length of LB samples was 22 mm (range, 20–25). The distribution of FT values according to maximal inflammatory activity in each fibrosis stage is shown in Table 2. The mean FT values increased significantly as fibrosis stage increased (0.23±0.17 for F1, 0.35±0.18 for F2, 0.59±0.21 for F3, and 0.71±0.21 for F4; all P<0.001 between each fibrosis stage) (Table 2 and Figure 2).

Using discriminant cutoff values to predict each fibrosis state (F1, F2, F3, and F4) by the FT (values were suggested in a previous study [13]), a discordance of at least two stages (gray) between the FT and LB is shown in Figure 2.
FT and LB was observed in 30 (9.1%) patients (Table 3). On the whole, using the FT, fibrosis stage was underestimated in 25 patients and overestimated in 5 patients with reference to LB (Table 3).

Factors Affecting the Discordance between Histology and FT Values

When we compared baseline characteristics of patients with nondiscordance and those with discordance, patients with discordance had a higher proportion of F3–4 (\(P = 0.001\)) and F4 (\(P = 0.012\)) than those with nondiscordance, with statistical significance (Table 4). The discordance rate was significantly higher in patients with F3–4 than in those with F1–2 (15.4% vs. 3.0%, respectively; \(P = 0.001\)) (Figure 3).

Subsequent multivariate analysis demonstrated that F3–4 at the time of LB was selected as the only independent factor for discordance between the two tests showing a positive correlation (\(P < 0.001\); adjusted OR, 5.95; 95% CI 2.22–15.96) (Table 5).

Influence of Histological Necroinflammation and ALT Level on FT Values

Although significant differences in necroinflammatory activity and serum ALT level between patients with discordance and those with nondiscordance were not detected (Table 4), previous studies of ultrasound-based tests such as transient elastography and ARFI [5,16,18] reported overestimation of fibrosis due to secondary effects of high ALT levels and/or necroinflammation. Thus, we further analyzed the influence of histological necroinflammation and ALT level in our cohort.

FT values between patients with maximal activity of grades 1–2 and 3–4 were statistically equivalent in each fibrosis stage (all \(P > 0.05\), Figure 4). In addition, there was no significant difference in FibroTest value between patients with normal ALT and those with high ALT in each fibrosis stage (all \(P > 0.05\), Figure 5).

Factors Affecting Discordance Based on External Cutoff Values

When we used the external cutoff values from BioPredictive (0.49, 0.59, and 0.75 for F \(\geq 2\), F \(\geq 3\), and F > 4, respectively), discords between the FT and LB were found in 41 (12.4%) patients; 36 patients were underestimated using the FT, whereas 5 patients were overestimated. Similarly, a higher proportion of patients with an advanced fibrosis stage (F3–4) were identified in patients with discordance (\(P < 0.001\)). On multivariate analysis, advanced fibrosis stage (F3–4) was the only predictor positively

Table 1. Baseline characteristics (n = 330).

| Variables                  | Value                  |
|----------------------------|------------------------|
| **Demographic data**       |                        |
| Age (years)                | 44 (20–83)             |
| Male gender                | 200 (60.6)             |
| Body mass index (kg/m²)    | 23.4 (15.1–35.8)       |
| Obesity (≥30 kg/m²)        | 9 (2.7)                |
| **Laboratory data**        |                        |
| Serum albumin (g/dL)       | 4.3 (2.9–5.4)          |
| Total bilirubin (mg/dL)    | 0.7 (0.2–2.0)          |
| Aspartate aminotransferase (IU/L) | 42 (12–385) |
| Alanine aminotransferase (IU/L) | 51 (5–551) |
| Prothrombin time (INR)     | 1.1 (0.91–1.25)        |
| Platelet count (10⁹/L)     | 186 (80–489)           |

Values are expressed as median (range) or no. (%).

INR, international normalized ratio.

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Figure 2. Box plots of FT values according to fibrosis stage. Mean FT values increase significantly as fibrosis stage increase (0.17 for F1 (range, 0.02–0.92), 0.35 for F2 (range, 0.05–0.94), 0.6 for F3 (range, 0.02–0.96), and 0.76 for F4 (range, 0.2–0.99), all \(P < 0.001\) among fibrosis stages).

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Table 2. Liver histology and corresponding FT values (n = 330).

| Fibrosis | FT value* | Maximal activity* | FT value* |
|----------|-----------|-------------------|-----------|
| Stage no. (%) | Mean ± SD | Grade no. Mean ± SD | Mean ± SD |
| 1        | 65 (19.7) | 0.23 ± 0.17       | 1         | 32 | 0.22 ± 0.18 |
| 2        | 103 (31.2)| 0.35 ± 0.18       | 1         | 11 | 0.35 ± 0.15 |
| 3        | 84 (25.5) | 0.59 ± 0.21       | 1         | 6  | 0.49 ± 0.16 |
| 4        | 78 (23.6) | 0.71 ± 0.21       | 1         | 7  | 0.75 ± 0.24 |

FT values* are described as mean ± standard deviation.

Maximal activity* grade was defined as the higher one between lobular and periportal activity.

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affecting discordance between the FT and LB ($P<0.001$; adjusted OR $9.31$, 95% CI $3.55$–$24.42$) (Table S1).

**Discussion**

The FT is known to show good diagnostic performance with reference to fibrosis stages of LB in not only the Caucasian population with CHC, but also Asian patients with CHB [10–13]. However, noninvasive surrogates for LB including the FT, no matter how they achieve their excellent diagnostic performance, are inherently subject to discordance compared with the fibrosis staging by LB primarily because noninvasive surrogates indirectly assess the total fibrotic burden instead of the architectural changes in liver parenchyma, which is the major factor in histological evaluation [19]. Nevertheless, because LB is the current gold standard, identification of factors associated with the discordance between noninvasive surrogates and LB is an important prerequisite for accurate assessment of the intrahepatic fibrotic burden. However, investigations on this issue are scarce so far, especially for the FT. In addition, data on the influence of necroinflammation on the FT value are lacking, which can be an important issue for two reasons: first, patients in whom LB is required usually have evidence of necroinflammation along with fibrotic burden; and second, probable effects (i.e., overestimation of fibrosis stage) of necroinflammation have been reported for several surrogate tests [5]. Therefore, our findings will assist formulation of guidelines for optimal evaluation of the intrahepatic fibrotic burden, ultimately avoiding underestimation or overestimation of the real fibrotic burden.

To our knowledge, this is the first study to investigate the prevalence of the discordance between LB and the FT and its predictors in Asian patients with CHB in a relative large cohort from three medical institutes. Advanced fibrosis (F3–4) at LB is a sole factor attributed to discordance between fibrosis stages by LB and the FT, indicating a greater chance of agreement between LB and the FT when patients with CHB show F0–2 at the time of LB. Indeed, most discordance in this study was caused by underestimation of liver fibrosis by the FT in patients with F3–4 (11 cases of F3 and 14 of F4 of 30 discordant cases). Furthermore, we analyzed the additional influence of histological necroinflammatory activity and serum ALT level on FT values in each fibrosis stage; neither affected either the likelihood of discordance or FT value itself. Interestingly, when we used the external cutoff values from BioPredictive, an advanced fibrosis stage of F3–4 was selected again as the only predictor of discordance.

In contrast to the FT, for transient elastography, a fibrosis stage of F0–2 is the only factor that predicts significant discordance with reference to LB in Asian patients with CHB, and necroinflammation (i.e., serum ALT level more than twice the upper normal limit) has been identified as a significant confounder, which nonspecifically increases liver stiffness values and thus leads to overestimation of the fibrosis stage [15–18,20]. Therefore, with active necroinflammation or ALT flares, measuring liver stiffness using transient elastography should be delayed after stabilization of necroinflammation and normalization of serum ALT to exclude such undesirable overestimating effects [21]. Such contradictory results of the FT and transient elastography are noteworthy in that they might be mutually complementary in assessing liver fibrosis in terms of combining the FT with transient elastography to enhance the diagnostic accuracy.

However, paradoxically, a histological stage of F0–2 favoring the use of the FT or F3–4 favoring the use of transient elastography cannot be revealed without LB. Therefore, the optimal diagnostic algorithm for use of these two noninvasive surrogates remains unresolved. The French guideline for

| Table 3. Distribution of fibrosis stages according to histology and FT. |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Fibrosis stage estimated by histology | Fibrosis stage estimated by FT | F1 | F2 | F3 | F4 |
| FT<0.32 | 0.32≤FT<0.52 | 0.52≤FT<0.68 | FT≥0.68 |
| F1 (n = 65) | 50 | 12 | | |
| F2 (n = 103) | 46 | 40 | 45 | 2 |
| F3 (n = 84) | | 11 | 36 | 25 |
| F4 (n = 78) | 8 | | 10 | 54 |
| Total (n = 330) | 115 | 70 | 92 | 83 |

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![Figure 3. Percentage of patients with non-discordance and those with discordance in fibrosis stage 1–2 (F1–2) vs. fibrosis stage 3–4 (F3–4). Patients with F3–4 had the significantly higher proportion of discordance than those with F1–2 (15.4% vs. 3.0%, $P<0.001$).](https://doi.org/10.1371/journal.pone.0055759.g003)
diagnosis of uncomplicated cirrhosis [22] is an example in which the FT and transient elastography are recommended as the first-line noninvasive diagnostic tools for liver fibrosis. In these guidelines, the fibrosis stage can be confirmed without LB for a given patient if the respective fibrosis stage based on the FT and transient elastography coincides, whereas LB is recommended when there is a discordant result in fibrosis staging between the FT and transient elastography. However, although this diagnostic strategy is based mostly on accumulated data from studies on CHC, it seems reasonable to combine the FT with transient elastography for enhanced diagnostic accuracy in assessing liver fibrosis in patients with CHB when we

| Variables                             | Patients with non-discordance (n = 300, 90.9%) | Patients with discordance (n = 30, 9.1%) | P value |
|---------------------------------------|-----------------------------------------------|----------------------------------------|---------|
| Clinical variables                    |                                               |                                        |         |
| Age (years)                           | 44 (20–83)                                    | 43 (24–65)                             | NS      |
| Male gender                           | 186 (62.0)                                    | 14 (46.7)                              | NS      |
| Body mass index (kg/m²)               | 23.5 (15.1–35.8)                              | 23.1 (18.7–31.3)                       | NS      |
| Obesity (≧30 kg/m²)                   | 7 (2.3)                                       | 2 (6.7)                                | NS      |
| Aspartate aminotransferase (IU/L)     | 42 (16–385)                                   | 38 (12–70)                             | NS      |
| Alanine aminotransferase (IU/L)       | 49 (7–551)                                    | 55 (5–157)                             | NS      |
| Platelet count (10^9/L)               | 186 (80–489)                                  | 175 (100–283)                          | NS      |
| Fibrosis stage                        |                                               |                                        |         |
| F2–4                                  | 238 (79.3)                                    | 27 (90.0)                              | NS      |
| F3–4                                  | 137 (45.7)                                    | 25 (83.3)                              | <0.001  |
| F4                                    | 63 (21.0)                                     | 14 (46.7)                              | 0.012   |
| Maximal activity⁴                     |                                               |                                        |         |
| A2–4                                  | 249 (83.0)                                    | 26 (86.7)                              | NS      |
| A3–4                                  | 107 (35.7)                                    | 9 (30.0)                               | NS      |
| A4                                    | 27 (9.0)                                      | 4 (13.3)                               | NS      |

Maximal activity⁴ grade was defined as the higher one between lobular and periportal activity. Values are expressed as median (range) or no. (%). doi:10.1371/journal.pone.0055759.t004

Table 5. Factors affecting discordance between FT and histology.

| Variables                             | Univariate | Multivariate |
|---------------------------------------|------------|-------------|
|                                      | P value    | Adjusted odds ratio (95% confidence interval) |
| Clinical data                         |            |             |
| Age (years)                           | NS         |             |
| Male gender                           | NS         |             |
| Body mass index (kg/m²)               | NS         |             |
| Aspartate aminotransferase (IU/L)     | NS         |             |
| Alanine aminotransferase (IU/L)       | NS         |             |
| Platelet count (10^9/L)               | NS         |             |
| Fibrosis stage                        |            |             |
| F4 (vs. F1–3)                         | 0.003      |             |
| F3–4 (vs. F1–2)                       | <0.001     | 5.95 (2.22–15.96) |
| F2–4 (vs. F1)                         | NS         |             |
| Maximal activity⁴                     |            |             |
| A4 (vs. A1–3)                         | NS         |             |
| A3–4 (vs. A1–2)                       | NS         |             |
| A2–4 (vs. A1)                         | NS         |             |

Maximal activity⁴ grade was defined as the higher one between lobular and periportal activity. NS, not significant. doi:10.1371/journal.pone.0055759.t005
consider the relatively lower performance of transient elastography in patients with CHB than in those with CHC [4]. The paucity of data regarding FT in patients with CHB and the increase in cost of addition of the FT should also be addressed in future studies.

This study has several strengths. First, a relatively large number of subjects from three medical institutes were consecutively enrolled, and the study population was homogenous and representative of patients with CHB generally seen in clinical practice. Second, because we recruited only patients who underwent baseline blood tests on the same day as LB, potential bias due to the gap between the two tests might have been prevented. Third, by demonstrating predictors of discordance between the FT and LB and proposing a rationale for combining several non-invasive surrogates to enhance the diagnostic accuracy, our findings will facilitate future studies that aim to propose a new noninvasive diagnostic algorithm for liver fibrosis in Asian patients with CHB.

However, we are also aware of several limitations of our study. First, there were no subjects with F0 fibrosis. Because three medical centers in this study are tertiary referral hospitals and one of the largest medical centers in Korea, patients with relatively more advanced disease are likely to be referred for close follow-up. This might have resulted in a selection bias and eventually a spectrum bias because the diagnostic performance of a given noninvasive test tends to increase in general in a cohort with high disease prevalence. Thus the diagnostic performances of FT might have been overestimated in our cohort. Therefore, another independent external validation study in a population with minimal fibrotic burden should be performed to provide more generalizable results in patients with CHB-related chronic liver disease. Second, we could not investigate the clinical role of the FT as a noninvasive monitoring tool to predict dynamic changes in liver fibrosis because a follow-up FT was not available. Third, although we identified predictors of discordance, it is unclear whether the long-term prognosis of patients with discordance differs from that of patients without discordance. In addition, whether we should follow the results of the FT or LB to start treatment intervention and predict the prognosis of a given patient is unclear. Clarification of these issues requires longitudinal studies using solid end-points such as hepatocellular carcinoma or liver-related death.

In conclusion, advanced fibrosis stage (F3–4) showed a positive correlation with discordance between LB and the FT in patients with CHB. Furthermore, necroinflammation and ALT levels were not factors predictive of accuracy. Future studies should focus on methods of enhancing the diagnostic accuracy of the FT in clinical practice.

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Supporting Information
Table S1  Factors affecting discordance between FT and histology by cutoff values from BioPredictive. (DOCX)

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Author Contributions

Patient management: JYP DYK SHA KHH CYC. Conceived and designed the experiments: MSP BKK SUK. Performed the experiments: MSP BKK SUK. Analyzed the data: MSP BKK JYC DJK SUK. Contributed reagents/materials/analysis tools: MSP BKK SUK. Wrote the paper: MSP BKK SUK.

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