To the Editor:

We read with interest the editorial on the correlation between hepatitis B virus (HBV) genotypes and outcome of HBV infection by Fung and Lok.1 This article made a succinct outline of the epidemiology of HBV genotypes and their association with hepatitis B e antigen seroconversion, activity of liver disease, and response to treatment. We believe that this article will be helpful to hepatologists when facing the explosion of knowledge regarding HBV genotypes in the literature.

However, the authors inferred from our previous data2 that genotype B may be associated with accelerated progression to hepatocellular carcinoma (HCC). This may be somewhat misleading, and we would like to address some comments to clarify this issue.

In Taiwan, our first cross-sectional study indicated that more than 50% of HBV-related HCC patients were infected with genotype B. In addition, genotype C was more prevalent in patients with HCC who were older than 50 years, whereas genotype B was more common in those with HCC who were age 50 years or younger. This predominance of genotype B was more substantial in younger patients with HCC, amounting to 90% among patients younger than age 35 years or younger, and most of them did not have cirrhosis. To confirm this preliminary observation from only 80 HCC patients, a further survey of 200 surgical cases showed that the prevalence of genotype C was indeed higher in older HCC patients, while that of genotype B was higher in young HCC patients.3 This observation also extends to HBV-related childhood HCC. In a recent study, we demonstrated that genotype B was still the major genotype (74%) in 26 children with HCC.4 Taken together, these lines of evidence strongly suggest that certain genotype B subtypes or strains are associated with the earlier development of HCC in Taiwan.

Thus, the genotype B strains in Taiwan may be different from those in Japan and China where HCC development is less frequent and occurs at an older age in patients with genotype B.5-7 We have proposed that genotype B can be divided into three phenotypes based on the rate of liver disease progression.8 The first is the slowly progressive phenotype that is associated with a tendency for early hepatitis B e antigen seroconversion during a carrier’s lifetime or in the course of chronic hepatitis, which subsequently leads to the low death rate from HCC. The second is the intermittently progressive phenotype that runs a typical natural course of chronic HBV infection with the development of HCC, usually in the patient’s 50s. The third is the rapidly progressive phenotype that is associated with the development of HCC in young HBV carriers before they reach 40 years of age, even in the absence of cirrhosis.

In summary, HBV genotypes do account for the heterogeneity in clinical manifestations and treatment response among patients with chronic hepatitis B in different parts of the world; however, the paradoxical findings of genotype predominance in HCC patients between Taiwan and other countries deserve further examinations.

JIA-HORNG KAO1,2,3
DING-SHINN CHEN2
1Hepatitis Research Center, Division of Gastroenterology
2Department of Internal Medicine
3Department of Medical Research
National Taiwan University Hospital
Taipei, Taiwan

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1. Fung SK, Lok AS. Hepatitis B virus genotypes: do they play a role in the outcome of HBV infection? HEPATOLOGY 2004;40:790–792.

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Benefit of TIPS for Patients With Refractory or Recidivant Ascites: Serum Bilirubin May Make the Difference

To the Editor:

The recent Italian trial of transjugular intrahepatic portosystemic stent shunt (TIPS) versus paracentesis for patients with refractory or recidivant ascites1 provides valuable information and stimulates considerations regarding the real value of TIPS for these patients. The study also adds to the three other large randomized trials recently published.2–4 These four studies, with a total of 305 patients, provide unanimous evidence that TIPS allows for much better control of ascites compared with repeated paracentesis: a complete response following TIPS has been observed in 51% to 79% compared with 3% to 24% in the paracentesis groups. Furthermore, quality of life is improved in patients with ascites after TIPS, particularly in patients with a complete response,5 supporting earlier investigations of quality of life after TIPS for various indications.6,7

However, the effect of TIPS on patient survival has been controversial. The present study5 confirms our previous observations2 and tips the balance toward improved survival. A North American trial5 found a nonsignificant trend in favor of TIPS, while a Spanish study4 clearly argued against a survival benefit for TIPS. How can these discrepant results be reconciled? The etiology of cirrhosis (alcoholic in 42% and 79% of the trials showing survival benefit2–4 vs. 51% and 62%, respectively, in the trials without survival benefit1–3) does not seem a likely explanation. Nor is the proportion of patients with Child-Turcotte-Pugh class C (76% and 38% vs. 37% and no detailed information in the Sanyal trial). Rather, we hypothesize that inclusion of patients with a serum bilirubin level above 3 mg/dL may make the difference. In our study,2 as well as in the Spanish trial,4 serum bilirubin was found to be an independent predictor of survival in multivariate and univariate analyses, respectively. The present study did not analyze bilirubin because it is a part of the MELD (model for end-stage liver disease) score, which was identified as a survival predictor by the authors.1 Interestingly, baseline serum bilirubin was also described as a powerful independent predictor of mortality after TIPS for variceal bleeding.8 Table 1 shows that in the Spanish trial, patients could be included with a serum bilirubin level of up to 10 mg/dL, whereas cutoff values were much lower for the other studies. Although the actual baseline values do not seem to differ much when given as mean and standard error, a closer look reveals that a substantial proportion of the Spanish trial must have been patients with a baseline bilirubin level greater than 3 mg/dL. Unfortunately, the exact percentage is only available in our trial (21%). Serum bilirubin concentrations 3 and 6 months after TIPS were increased in all studies. Interestingly, however, the variation is much lower in the trials with survival benefit1–4 compared with the studies showing no benefit.5–4 Judging from the mean values and standard error provided, some patients in the Spanish and United States trials had serum bilirubin levels above 12 mg/dL 6 months following TIPS. Not surprisingly, liver failure was reported as the most common cause of death in these studies.

Another aspect deserves attention. All studies were analyzed as intent-to-treat and allowed for crossover of treatments. Interestingly, the proportion of patients randomized to paracentesis but ultimately receiving TIPS was higher in the Italian and German trials (11 of 33 and 10 of 31, respectively) than in the other two studies (3 of 35 and 2 of 57). Thus, one may speculate that the actual benefit of TIPS may be even higher than demonstrated. Altogether, the publication by Salerno et al.1 is in accordance with our contention that TIPS may be particularly useful for patients with massive ascites and serum bilirubin levels below 3 mg/dL.

ALEXANDER L. GERBES
VEIT GÜLBERG
Department of Medicine II
University of Munich-Großhadern
Germany

References

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Table 1. Bilirubin Serum Concentrations (mg/dL) in TIPS Trials (Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Italian1</th>
<th>German2</th>
<th>Spanish4</th>
<th>U.S.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoff for study inclusion</td>
<td>6</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.6 ± 0.1</td>
<td>1.7 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2.1 ± 0.2</td>
<td>2.9 ± 0.9</td>
<td>4.6 ± 2</td>
<td>2.2 ± 2.1</td>
</tr>
</tbody>
</table>

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Dietary Fiber Decreases Ammonia Levels in Patients With Cirrhosis

To the Editor:

We read with interest the paper by Liu et al. recently published in HEPATOLOGY in which they demonstrated that oral coadministration of fermentable fiber and live bacteria significantly improved gut flora, plasma ammonia levels, neuropsychological tests, endotoxemia, and the Child-Turcotte-Pugh score in patients with liver cirrhosis.1 They also demonstrated that fermentable fiber alone has similar therapeutic benefit. They assessed the effect of fermentable fiber by quantitative bacteriological and pH analysis of fecal samples.1 We have also under-

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Table 1. Changes in Blood Tests and Nutritional Element in Food Intake Before and After Fermentable Fiber Therapy

<table>
<thead>
<tr>
<th>Nutritional Element in Food Intake</th>
<th>Fiber Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At entry</td>
<td>After 30 days</td>
</tr>
<tr>
<td>Energy (kcal)</td>
<td>1618 ± 203</td>
<td>1659 ± 235</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>58 ± 12</td>
<td>63 ± 13</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>40 ± 10</td>
<td>40 ± 7</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>256 ± 32</td>
<td>269 ± 51</td>
</tr>
<tr>
<td>Fiber (g)</td>
<td>12 ± 5</td>
<td>26 ± 6*</td>
</tr>
</tbody>
</table>

NOTE. Data are mean ± standard deviation. Abbreviation: Ch-E, cholinesterase.

*P < .05 vs. data at entry.

References
2. Rokkas T, Vaja S, Murphy GM, Dowling RH. Postheparin plasma diaphorase activity. A decrease in pH with SCFA production in large intestine also appears to improve plasma ammonia levels. Fermentable fiber intake may be a supplementary treatment for patients with cirrhosis.