It is likely that the consequences of the multiple immune reactions induced by the presence of bacterial DNA may be indeed different according to the field of research. Patients with advanced cirrhosis are characterized by a marked immune and hemodynamic instability. This fact makes them even more sensitive to the presence of bacterial DNA and likely other bacterial products that may further promote instability than patients without cirrhosis. According to our level of actual knowledge, it is not possible to assess which, among many, are the main reasons promoting a poor prognosis in patients with presence of bacterial DNA. New and multiple lines of research will be needed to answer these and probably many other questions that will likely arise in the future.

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Insulin Resistance and Platelet Count/Spleen Diameter Ratio: Two Simple, Easy-to-Get Tests for Predicting Esophageal Varices in Cirrhosis

To the Editor:

We read with great interest the article by Cammà et al.[1] reporting the potential usefulness of insulin resistance (IR) combined with platelet count/spleen diameter ratio as simple, noninvasive, and easy-to-get tests for predicting esophageal varices (EVs) in patients with Child A cirrhosis caused by hepatitis C virus (HCV). We would like to draw attention to similar studies on IR combined with platelet count/spleen diameter ratio in predicting EVs in cirrhosis, not just in Child A HCV cirrhosis.

Platelet count/spleen diameter ratio as a noninvasive diagnosis test for EVs in cirrhosis,[2] including HCV cirrhosis,[3] has been widely used in clinical practice for many years. The usefulness of IR in cirrhosis is also not surprising, because recent studies have revealed a close relationship between IR and the progression of chronic liver disease,[4] including the fibrosis progression of chronic hepatitis C.[5] We tested 349 patients with cirrhosis in our center, including Child A (123 patients), Child B (112 patients), and Child C (114 patients). Compared to the study by Cammà, which reported that a low platelet count/spleen diameter ratio (95% confidence interval [CI], 0.996-0.999) and a high homeostasis model assessment of insulin resistance (HOMA-IR) score (95% CI, 1.018-1.649) could be used to predict the presence of EVs, we found a very similar result in our cohort and also confirmed it in another independent cohort. Further, we also found the HOMA-IR score has a positive correlation with a worsening of the hepatic function. The HOMA-IR score in the Child C group (5.13 ± 0.29) is significantly higher than that of the Child B group (3.39 ± 0.33, $P < 0.05$) and the Child A group (2.66 ± 0.15, $P < 0.05$). However, multivariate analysis showed that the 95% CI of the two indexes in Child A HCV cirrhosis in our cohort (Platelet count/spleen diameter ratio: 95% CI, 0.989-0.994; HOMA-IR score, 95% CI, 1.125-1.757) are somewhat different than that of the report by Cammà et al. (95% CI, 0.996-0.999 versus 95% CI, 1.018-1.649, respectively).

In summary, our data highlight three points. First, we show that the IR combined with platelet count/spleen diameter ratio could be used as useful markers to predict EVs in cirrhosis, partially concurring with the findings from the study by Cammà et al. Second, compared with the study by Cammà et al., we show the differential 95% CI of IR and platelet count/spleen diameter ratio in the Chinese population. Differences in results between the two studies are likely to derive from ethnic/geographical variations. Third, considering that the reference intervals of the two indexes may be affected by other factors such as age, sex, and ethnicity, further studies on large, multicenter cohorts are needed to search the appropriate reference intervals in differential ethnic/geographical groups.

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Reply:

In their letter, Dr. Li and colleagues add further evidence to the fact that insulin resistance (IR) may be used as a surrogate noninvasive marker to predict the presence of esophageal varices (EVs). They first validated, in a large training set of 349 Chinese patients with cirrhosis of mixed etiology and stage, homeostasis model assessment (HOMA) and platelet count/spleen diameter ratio as independent predictors of EV presence in patients with Child class A, B, and C cirrhosis, and then confirmed these results in another independent test set. Results comparable to ours[1] were obtained in the subgroup of patients with hepatitis C virus (HCV)-derived Child A cirrhosis.

Dr. Li and colleagues found a positive relation between HOMA and liver function, which is to be expected given the reduced liver function in patients with Child B and C cirrhosis. In our study,[1] to exclude confounding factors for HOMA evaluation such as hepatic failure and "hepatogenous diabetes",[2] we included only patients with Child A cirrhosis.

Li et al. remark that in their cohort the 95% confidence interval of the two predictors are somewhat different compared from those of our study. These differences could be related not only to ethnic/geographical variations, as they suggest, but also to the differences in prevalence of EVs in the study population, to the etiology of cirrhosis, and to the different metabolic and anthropometrical features of the patients. In the letter, no information is given about anthropometric parameters and prevalence of

diabetes in the study population. This is of major relevance, considering that HOMA is not a reliable index of IR in diabetic patients on insulin therapy. Furthermore, they do not report the etiology of cirrhosis in their patients. In our study,[1] we included only HCV-infected patients because much clinical and experimental evidence suggests that HCV by itself is able to interfere with insulin signaling.[3] Furthermore, in the setting of chronic HCV infection, IR has been associated with progression of fibrosis.[4] Some of the clinical expression of IR, namely obesity and diabetes, correlate with an increased risk of hepatocellular carcinoma.[5]

It would be interesting to know whether, in the Chinese population, IR is associated to presence of EVs not only in cirrhosis derived from HCV, but also from nonalcoholic fatty liver disease cirrhosis, where IR is the pathogenetic key of the disease,[6] and in patients with hepatitis B virus (HBV), considering recent experimental data suggesting the potential ability of HBV to interfere with nuclear receptors involved in liver lipid homeostasis.[7]

In conclusion, it must be stressed that in any population of patients, prediction rules—although valuable in predicting the average probability of specific events in a group of patients—are much less accurate in predicting the outcome in individual patients. Although confident that HOMA and platelet count/spleen ratio are useful to predict EV, we feel that to reach a degree of precision useful for the clinician, these predictors should probably be combined with other noninvasive screening tools, such as transient fibroelastometry.[8]

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A Crossing in Therapy for Hepatitis C Virus Genotype 2 or 3: Increasing Ribavirin Dose with Shortened Duration or Reducing Ribavirin Dose with Standard Duration

To the Editor:

We read with great interest the article in a recent issue of HEPATOLOGY.[1] Ferenci et al. reported that 68.8% (97/141) and 63.8% (90/141) of treatment-naïve patients infected with hepatitis C virus (HCV) genotype 2 or 3 (HCV-2, HCV-3) achieved a sustained virological response (SVR) after 24 weeks of treatment with ribavirin 800 mg/day (group A) and 400 mg/day (group B), respectively, plus peginterferon alfa-2a (PegIFN) 180 μg/week. In group A more than group B patients, the rate of SVR was similar among patients infected with HCV-3 (67.5% versus 63.9%), but the rate of SVR was significantly higher (77.8% versus 55.6%) among patients infected with HCV-2. The authors concluded that when administered for 24 weeks with PegIFN, ribavirin doses of 400 and 800 mg/day produce equivalent outcomes in patients infected with HCV-3.

Rapid virological response (RVR), defined as achieving seronegativity for HCV RNA at week 4 of treatment, has become the most important virological factor in predicting response to the treatment of chronic hepatitis C.[2] In spite of standard therapy for 24 weeks, shortening the duration of combination therapy for patients infected with HCV-2 or HCV-3 with RVR has been suggested recently. Among patients with RVR, shortened regimens with higher dose of ribavirin per body weight had considerably higher rates of SVR than that with lower dose of ribavirin exposure by body weight (90%-100% versus 71%-79%, respectively).[3-6] Di Martino et al. have reported the effect of a 16-week course of therapy together with a weight-based ribavirin regimen that seems equivalent to a 24-week treatment duration with fixed dosing of ribavirin at 800 mg/day.[7] The rates of RVR were higher with a higher dose of ribavirin per body weight (78%-93%)[3,4,8] when compared to that with lower doses of ribavirin per body weight (62%-65%).[5,6] Furthermore, low body weight,[9] higher ribavirin dose,[10] and the first 4 weeks of weight-based ribavirin exposure (>13 mg/kg/day)[11] have been associated with the achievement of an RVR. These reports implicate that providing optimal dose of weight-based exposure of ribavirin is pivotal in the treatment of chronic hepatitis C. Although ribavirin doses of 400 and 800 mg/day produce equivalent efficacy in the study by Ferenci and coworkers,[1] it raises concerns that reduced dose to fixed 400 mg/day (5.5 mg/kg/day) or even 800 mg/day (11.3 mg/kg/day) of ribavirin possibly are "suboptimal" doses to achieve a maximum RVR rate. On the other hand, the regimen with shortened duration and weight-based ribavirin dose has reduced the cost compared to 400 or 800 mg/day regimen for 24 weeks. Taken together, further studies are warranted, when we face the choice in the treatment of patients with HCV-2 or HCV-3 with RVR, to shed light on the alternatives of either shortening the duration with weight-based ribavirin dose or reducing the ribavirin dose with 24 weeks duration.

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