CORRESPONDENCE

Evolution of Intrapulmonary Vascular Dilatations in Cirrhosis

To the Editor:

Intrapulmonary vascular dilatations (IPVD), diagnosed by transthoracic contrast-enhanced echocardiography (CEE), can be observed in 13% to 47% of individuals with liver cirrhosis.[1,2] Despite the presence of IPVD, most patients are not characterized as having hepatopulmonary syndrome (HPS), since the diagnosis of this syndrome requires the presence of abnormal arterial oxygenation (partial pressure of arterial oxygen < 70 mm Hg, or alveolar arterial oxygen gradient > 20 mm Hg).[3,4] One of the major controversies is whether cirrhotic individuals with IPVD but without changes in arterial oxygenation are affected by HPS in the early phase and whether these alterations would appear during follow-up.[5] To our knowledge, there are no prospective studies of the evolution of pulmonary parameters in cirrhotic individuals with IPVD but without changes in arterial oxygenation. Would these patients fulfill HPS criteria during follow-up?

In our series[6] of 56 cirrhotic patients on a waiting list for orthotopic liver transplantation, the frequency of IPVD was 45% (25 patients). Among these patients, 16 (64%) did not fulfill the criteria for HPS, confirming the high frequency of IPVD in cirrhotic subjects without HPS. These patients were followed prospectively to assess the evolution of pulmonary parameters. Of 16 cirrhotic patients with IPVD without changes in arterial oxygenation, 12 were excluded from the study, 11 due to death (after exploratory laparotomy [1], cancer of the larynx [1], digestive hemorrhage [5], spontaneous bacterial peritonitis [2], orthotopic liver transplantation [1 sepsis and 1 hemorrhage]) and 1 because he was submitted to orthotopic liver transplantation. Mean follow-up of the excluded patients was 13.8 months (2–28 months). The complementary tests were not repeated in any of the excluded patients. Thus, the final series consisted of 4 patients with a mean follow-up of 24 months (21–30 months). All patients were submitted to contrast-enhanced echocardiography and measurement of arterial blood gases at the beginning and at the end of follow-up. The results are presented in Table 1. The contrast-enhanced echocardiography remained positive in all patients. No patient presented significant changes in arterial oxygenation that would characterize him as having HPS. The present data suggest stability of the pulmonary parameters during the 2-year follow-up period.

The causes of the high mortality rate of our patients did not seem to be related to the presence of HPS, both because of the absence of pulmonary causes and because of the short period of time between the diagnosis of IPVD and death. Schenk et al.[7] demonstrated that not only the presence but also the severity of HPS are related to the survival of cirrhotic patients. It should be emphasized that our patients did not have HPS nor did they present alterations in gas exchanges. In addition, our patients with HPS[6] tend to have mild degrees of the syndrome, in contrast to the data reported by Schenk et al.[7] However, although this is unlikely, we cannot exclude the possibility of progression to HPS in the patients who died. In conclusion, the present results suggest that gas exchange abnormalities did not develop uniformly and IPVD persisted during a mean follow-up of 24 months.

Table 1. Blood Gas Measurements and Evaluation of IPVD in the 4 Patients Studied

		Patient 1	Patient 2	Patient 3	Patient 4
PaO_2 (mm Hg)	Baseline	93.4	96.9	92.4	85.9
	End	97.5	95.6	94.8	85.0
$AaPO_2$ (mm Hg)	Baseline	17.8	5.3	13.6	17.4
	End	14.2	18.5	16.8	18

Abbreviations: PaO_2, partial pressure of arterial oxygen; $AaPO_2$, alveolar arterial oxygen gradient.

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Long-Term Outcome of Hepatitis C in Children

To the Editor:

We have read with interest the paper by Casiraghi et al.[1] concluding that hepatitis C virus (HCV) infection acquired early in life (through blood transfusions) shows mild features and a slow progression during the first 35 years after exposure. Similar results came from previous retrospective studies in adults transfused early in life for cardiac surgery or for leukemia.

Chronic HCV infection is generally associated with mild liver disease during the first two decades of life in both transfused and perinatally infected children. Nevertheless, recent data in the literature and our own experience suggest the need for caution regarding the prognosis of HCV infection acquired in childhood. Regarding the short-term prognosis, cases of severe hepatitis and cirrhosis can be seen throughout childhood and adolescence in children without underlying diseases. About 7% to 10% of Italian children with chronic hepatitis C develop liver-kidney microsomal autoantibodies, and we could observe that liver disease is more severe and progressive in these patients than in a comparable population of HCV-infected children without serological markers of autoimmunity.[2] Also, we have recently seen 3 children who had developed compensated cirrhosis in the first decade of life, apparently in the absence of known comorbid conditions and autoimmunity. All 3 were male, with alanine aminotransferase levels greater than twice the normal throughout observation, and with history of maternal drug abuse. Only one mother was coinfected with human immunodeficiency virus (HIV). Birnbaum et al.[3] reported 3 similar cases, ages 4–11 years, but with decompensated cirrhosis and with evidence of HIV coinfection in 2 of 3 mothers (abuse was not disclosed). Maternal HIV/HCV coinfection and maternal drug abuse are independent risk factors for vertical HCV transmission; drug abuse seems to favor HCV infection of maternal peripheral blood mononuclear cells, which in turn would transmit the infection from mother to offspring.[4] Whether these early events may have relevance on the outcome of infection and disease remains to be elucidated. Nevertheless we are closely following HIV-seronegative children with high alanine aminotransferase levels and history of maternal abuse and/or HIV coinfection.

Regarding medium/long-term prognosis, it appears that older adolescents and young adults have higher rates of liver fibrosis than do younger children, independent of comorbid conditions, and we have recently shown increasing rates of fibrosis in serial biopsies of children on long-term follow-up.[5] Casiraghi et al.[1] show that virus replication is maintained for decades in their patients; thus progression of liver disease could occur at any time, especially considering that exposure to cofactors of liver damage increases in youth and adulthood.

Following these considerations, we hope that the apparently benign profile of pediatric HCV infection will not discourage or delay research in the therapy of this disease, taking into account that children have a long life expectancy, and that an efficient and well-tolerated treatment regimen would be cost-effective.

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Reply:

We appreciate the letter of Bortolotti et al. and the update on their results regarding the prognosis of hepatitis C virus (HCV) infection acquired in childhood, either through transfusion or by the vertical/perinatal route. We agree that hepatitis C is not always an innocuous disease in childhood, and that cirrhosis and extensive fibrosis may occur in some children even in the absence of comorbidities.[1,2] The authors indicate that liver disease may be more severe and progressive in children with liver/kidney microsomal antibody type 1 autoantibodies compared to those without serological markers of autoimmunity.[3] In addition, they suggest that maternal coinfection with human immunodeficiency virus and HCV, as well as maternal drug use, both independent risk factors for vertical transmission,[4] might have a role in worsening the outcome of HCV infection acquired perinatally.

Our data concern the long-term outcome (35 years) of HCV infection in a unique cohort of individuals who acquired HCV through mini blood transfusions derived from an HCV-infected donor.[5] All recipients were infected with the same virus genotype (1b), at the same time (shortly after birth) and with the same volume of infectious blood (21–30 mL), and were specifically traced through the clinical files of the hospital in which they were born. None of our HCV-infected individuals were liver/kidney microsomal antibody type 1 -positive and none had comorbid conditions such as hepatitis B virus or human immunodeficiency infection, or alcohol intake (>50 g per day). Moreover, none of the individuals enrolled in this study were aware of having been transfused and infected during the first weeks of life, and only one (who was a drug user) had additional risk factors for HCV infection. Therefore, it would seem that the differences in the outcome of HCV infection acquired in childhood, observed in our and other studies, may be due to differences in the population examined.

Taking into account the above findings, one could expect subgroups of children (*i.e.,* those born to HCV-carrier mothers who are coinfected with human immunodeficiency virus and/or are drug users, and those with autoimmune abnormalities) who are at increased risk of developing severe liver disease and even cirrhosis early in life. However, the role of these determinants in heralding a more aggressive outcome in HCV-positive children requires further investigation.

Finally, we fully agree with our colleagues that the apparent benign course of HCV infection seen in most children does not imply that treatment should be delayed or even unwarranted in childhood, and that the research of novel, well-tolerated, and effective therapeutic strategies should remain a priority.

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Does Noninvasive Staging of Fibrosis Challenge Liver Biopsy as a Gold Standard in Chronic Hepatitis C?

To the Editor:

Liver biopsy is viewed as the gold standard for staging fibrosis in chronic hepatitis. An ongoing great search for noninvasive diagnostic tests aims at replacing this inconvenient and costly invasive procedure. Several models have been proposed[1–3]; however, most of them require special laboratory parameters that are not available in clinical practice. In a recent article, Wai et al. proposed a simple model on the basis of routinely available laboratory test results (aspartate aminotransferase–to-platelet ratio index, [APRI]), which was shown to predict with high sensitivity and specificity liver fibrosis in patients with hepatitis C virus infection.[4] These results were recently challenged by Giannini and Testa, who pointed out that the ratio of aspartate aminotransferase to alanine aminotransferase assessed fibrosis more accurately than the APRI.[5]

We would like to comment on the applicability and validity of the APRI test, which we have applied to a large cohort of 484 treatment naive patients with chronic hepatitis C (271 males; mean age, 46 ± 0.4; range, 18-68 years). All patients underwent liver biopsy as part of the screening evaluation within the course of national or international clinical trials. Staging of fibrosis was done according to the Scheuer[6] score, which categorizes 4 different stages of fibrosis (F0-F4), as compared to the Ishak score used by Wai et al. referring to 6 stages (F0-F6).

Our results are in agreement with the data presented by Wai et al., although the overall sensitivity and specificity of the APRI as well as the positive predictive value and the negative predictive value for the certain cutoffs were found to be lower (Table 1). As mentioned, the different histological scoring system (*i.e.,* Scheuer vs. Ishak score) could be responsible for these differences. Additionally, our results have been evaluated by several pathologists, not by just one as in the Wai et al. study. Interobserver differences certainly could have played a role in this respect, but in clinical practice one is confronted with this kind of situation.

From these studies it appears that fibrosis stage assessed by invasive and noninvasive approaches differ to some extent. In this respect, sampling variability and the size of liver biopsies have to be considered as important contributors to false fibrosis staging,[7] and they raise the question of whether liver biopsy can still be regarded as the gold standard for fibrosis assessment. Thus, the interpretation of liver biopsy results on the background of a noninvasive fibrosis prediction method should be proven as a rational approach to improve accuracy of fibrosis staging. One should, however, be aware that a reliable noninvasive assessment of the different stages of fibrosis cannot be made in all patients. Data by Wai et al. as well as our data are in accordance, showing that a prediction concerning presence or absence of significant fibrosis was possible only in 57% and 51%, respectively, of the patients examined in both studies.

Finally, the need to confirm histologically the stage of fibrosis is suspect when clinical experience and laboratory data provide all necessary information to judge with great certainty the severity of patients' chronic liver disease.

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Table 1. Accuracy of the AST-to-Platelet Ratio Index (APRI) in Predicting Significant Fibrosis and Cirrhosis

APRI*	All Patients (n = 484) n (%)	Actual Fibrosis† Stage 0–1 (n = 231) n (%)	Actual Fibrosis† Stage 2–4 (n = 253) n (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
For prediction of significant fibrosis							
≤0.50	168 (35)	122 (53)	46 (18)	82 (91)‡	53 (47)‡	66 (61)‡	73 (86)‡
>0.50	316 (65)	109 (47)	207 (82)				
≤1.50	375 (77.5)	215 (93)	160 (63)	37 (41)‡	93 (95)‡	85 (88)‡	57 (64)‡
>1.50	109 (22.5)	16 (7)	93 (37)				
		Actual Fibosis Stage 0–2 (n = 357)	Actual Fibosis Stage 3–4 (n = 127)				
For prediction of cirrhosis							
≤1.0	325 (67)	286 (80)	39 (31)	69 (89)§	80 (75)§	55 (38)§	88 (98)§
>1.0	159 (33)	71 (20)	88 (69)				
≤2.0	409 (84.5)	332 (93)	77 (61)	39 (57)§	93 (93)§	67 (57)§	81 (93)§
>2.0	75 (15.5)	25 (7)	50 (39)				
		Actual Fibrosis Stage 0–3 (n = 422)	Actual Fibrosis Stage 4 (n = 62)				
≤1.0	325 (67)	310 (73.5)	15 (24)	76 (89)§	73.5 (75)§	30 (38)§	95 (98)§
>1.0	159 (33)	112 (26.5)	47 (76)				
≤2.0	409 (84.5)	377 (89)	32 (52)	48 (57)§	89 (93)§	40 (57)§	92 (93)§
>2.0	75 (15.5)	45 (11)	30 (48)				

Abbreviations: AST, aspartate aminotransferase; PPV, positive predictive value; NPV, negative predictive value.

*Results are given according to the APRI cutoff points proposed by Wai et al. to predict the absence (APRI ≤ 0.50) or presence (APRI >1.50) of significant fibrosis and the absence (APRI ≤1.00) or presence (APRI >2.00) of cirrhosis.

†Staging of fibrosis was done according to the Scheuer score, which categorizes 4 different stages of fibrosis (F0, absent; F1, mild portal fibrosis without septa; F2, moderate portal fibrosis with few septa; F3, numerous septa [bridging fibrosis] without cirrhosis; F4, cirrhosis), as compared to the Ishak score used by Wai et al. referring to 6 stages (F0–F6). Significant fibrosis was defined as ≥F2. Data for prediction of cirrhosis were given for patients histologically classified as either F3–F4 or F4.

‡§Respective data for sensitivity and specificity as well as the positive and negative predictive value assessed in the study by Wai et al. for patients with Ishak fibrosis scores F0–2 vs. F3–6‡ and 5–6 vs. F0–4§ are shown in parentheses.

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Reply:

We thank Berg et. al. for the interest expressed on our article.[1]

We are grateful that many investigators like Berg et. al. had tested our prognostic model in their patient populations.[2,3] Using the *aspartate aminotransferase to platelet count ratio index* (APRI), significant fibrosis could be identified or excluded in 57.5% of Berg's patients with 82% sensitivity and 93% specificity, and cirrhosis could be identified or excluded in 82.5% of patients with 69% sensitivity and 93% specificity. The specificities were almost identical to those in our study, while the sensitivities were lower. The proportion of patients who fell into the classifiable group was higher than in our study. We agree that the diminished sensitivities may be related to the use of a different fibrosis scoring system, as well as multiple versus single pathologists scoring the biopsies. It is also possible that the inclusion of stage 3 in the Scheuer[4] scoring system (fibrosis with architectural distortion but no obvious cirrhosis) as cirrhosis may have affected the accuracy of prediction of cirrhosis.

We agree that interobserver or intraobserver variability and size of the biopsies may affect histological interpretation. Because liver biopsies are not necessarily gold standards for assessing liver histol-

ogy, noninvasive models will not have complete concordance with histological staging. We agree that neither liver biopsy nor noninvasive model is necessary when the severity of the patients' chronic liver disease is obvious, as in the case of patients with decompensated cirrhosis. However, differentiating mild from moderate fibrosis, and moderate fibrosis from well-compensated cirrhosis may be difficult even for experienced hepatologists. Thus, there remains a role for simple noninvasive models that will help in providing more reliable estimates of the stage of liver disease than a clinician's intuition.

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High Sensitivity C-Reactive Protein Values Do Not Reliably Predict the Severity of Histological Changes in NAFLD

To the Editor:

C-reactive protein is an acute phase reactant that has found widespread application in clinical medicine as a predictor of cardiovascular events.[1] High sensitivity C-reactive protein (hsCRP) detects low-grade systemic inflammation. Levels of hsCRP are raised in disorders associated with nonalcoholic fatty liver disease (NAFLD), including obesity[2] and features of the insulin resistance syndrome (hypertriglyceridemia, low HDL cholesterol, raised glucose level).[3] In NAFLD, the differentiation of simple steatosis from nonalcoholic steatohepatitis (NASH) is clinically important. Steatosis alone tends to have a benign course, whereas NASH may progress to cirrhosis, liver failure, and hepatocellular carcinoma.[4,5] At present, there is no specific clinical or biochemical marker to distinguish the two entities. We therefore examined the utility of hsCRP levels in differentiating simple steatosis from NASH, and for predicting the severity of hepatic necroinflammation.

We measured hsCRP in 120 persons (IMMAGE CRPH, Beckman Coulter, CA; lower detection limit = 0.2 mg/L).[6] Those with CRP >10 (n = 12, including 3 with no necroinflammation) may have had subclinical infections or minor traumas and were therefore excluded from analysis.[7] NASH (n = 75) was distinguished from simple steatosis (n = 33) by the presence of lobular inflammation, and either ballooning cells or perisinusoidal/ pericellular fibrosis in zone 3 of the hepatic acinus.[4] The severity of steatosis, necroinflammation and fibrosis were graded using the method of Brunt et al.[8]

Similar to previous reports, there were significant associations between the hsCRP levels and age ($r = 0.2$, $P = .01$), body mass index ($r = 0.5$, $P < .01$), waist-to-hip ratio ($r = 0.4$, $P = .001$), and insulin resistance by homeostasis model ($r = 0.2$, $P = .04$).[7] However, no relationship was discerned between the levels of hsCRP and the grades of hepatic steatosis ($r = 0.2$, $P = .1$), necroinflammation ($r = 0.1$, $P = .4$), and fibrosis ($r = 0.1$, $P = .5$). The mean (±SD) hsCRP for NASH was 2.68 ± 2.10 mg/L, and 2.23 ± 1.68 mg/L for simple steatosis ($P = .4$).

In this cohort, measurement of hsCRP was not useful in predicting the histological severity of NAFLD. It has been shown that hsCRP levels are strongly associated with body mass index and insulin resistance,[9] and 56% of our cohort were obese and insulin resistant. On the other hand, the use of 3-hydroxy-3-methylalutaryl coenzyme A (HMG-CoA) reductase inhibitors is known to reduce hsCRP levels,[10] and 29% of our subjects were taking these agents. In the presence of such confounders, the use of a multivariate model with a much larger sample size is required to detect an effect of hepatic necroinflammation on hsCRP levels. If the population parameters for hsCRP in patients with NAFLD are similar to those observed in the present report, a sample size of over 400 subjects per group will be required to have 80% power to detect a statistically significant difference between simple steatosis and NASH. Clearly, a multicenter collaborative approach is needed to undertake such a study. However, we conclude that the clinical utility of hsCRP is limited by the extent of overlapping values in patients with NASH and simple steatosis.

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