Validity and Clinical Utility of the Aspartate Aminotransferase–Alanine Aminotransferase Ratio in Assessing Disease Severity and Prognosis in Patients With Hepatitis C Virus–Related Chronic Liver Disease

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Background: The aspartate aminotransferase–alanine aminotransferase ratio (AST/ALT ratio) has been used to noninvasively assess the severity of disease in patients with chronic liver disease (CLD). We previously demonstrated that progressive liver functional impairment is associated with an increase in the AST/ALT ratio.

Objectives: To evaluate the reproducibility and transportability of the AST/ALT ratio in a large cohort of patients with different degrees of hepatitis C virus (HCV)–related CLD, to confirm the correlation between progressive impairment of liver function and increase in the AST/ALT ratio, to evaluate whether diagnostic accuracy of the ALT/AST ratio can be improved by using it with other biochemical variables, and to assess the 1-year prognostic capability of the AST/ALT ratio in patients with liver cirrhosis.

Patients and Methods: We retrospectively evaluated 252 patients with HCV-related CLD. The AST/ALT ratio was correlated with the degree of liver fibrosis in patients with chronic hepatitis and with the Child-Pugh score in patients with cirrhosis. All patients had undergone monooethylglycinexylidide (MEGX) testing to evaluate liver function. We assessed the prognostic ability of the AST/ALT ratio in a subset of 63 cirrhotic patients who were followed up for at least 1 year.

Results: The AST/ALT ratio was more frequently 1 or higher in cirrhotic patients (P<.001). There was a significant correlation between MEGX values and the AST/ALT ratio (r = −0.621, P<.001). Multivariate stepwise logistic analysis showed that AST/ALT ratio, platelet count (PLT), MEGX values, and prothrombin activity were independently associated with the presence of cirrhosis. Combined assessment of the AST/ALT ratio and/or PLT obtained 97.0% positive predictive value and 97.9% negative predictive value for the diagnosis of cirrhosis. The AST/ALT ratio had 81.3% sensitivity and 55.3% specificity in identifying cirrhotic patients who died within 1-year of follow-up.

Conclusions: The AST/ALT ratio is both reproducible and transportable in patients with HCV-related CLD. The AST/ALT ratio is correlated with both histologic stage and clinical evaluation. Progressive liver functional impairment is reflected by an increase in the AST/ALT ratio. Noninvasive evaluation by means of the combined AST/ALT ratio and PLT assessment misclassifies only a few cirrhotic patients. In cirrhotic patients, the AST/ALT ratio provides medium-term prognostic information that is no different from that provided by established prognostic scores.

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epidemiologic and ethnic backgrounds. Nevertheless, the use of the AST/ALT ratio as a clinical decision aid in patients with chronic HCV infection has recently been a matter of debate.13-16 In a previous study performed on a large population of patients with CLD of various origins, we showed that a progressive increase in the AST/ALT ratio is correlated with a concomitant decrease in liver function and that an AST/ALT ratio of 1 or higher has good specificity and sensitivity for the diagnosis of cirrhosis.17 More recently, we demonstrated that the AST/ALT ratio replicates its accuracy in a set of patients not included in our prior study17 but who represent the same population (ie, reproductibility) and produces accurate predictions in a different but related population (ie, transportability).15

Most of the patients with HCV-related chronic hepatitis undergo antiviral therapy, and therefore it would be unfeasible to evaluate the AST/ALT ratio as a prognostic tool in these patients since the natural history of the disease is in some way modified by treatment. However, the utility of the AST/ALT ratio as a prognostic tool in patients with HCV-related cirrhosis has not yet been considered and compared with well-defined and accepted prognostic scores, such as the Child-Pugh score or the Model for End-stage Liver Disease (MELD).18

Thus, the aims of this study were as follows: (1) to assess the reproducibility and transportability of the AST/ALT ratio in a large cohort of patients with different degrees of CLD related to HCV infection alone, (2) to confirm the correlation between the progressive impairment of liver function and the increase in the AST/ALT ratio in these patients, (3) to evaluate whether the accuracy of the AST/ALT ratio in the noninvasive diagnosis of cirrhosis can be improved by using it with other variables, and (4) to estimate the 1-year prognostic ability of the AST/ALT ratio compared with the Child-Pugh and the MELD scores in patients with HCV-related cirrhosis.

METHODS

We retrospectively analyzed 252 patients with varying degrees of HCV-related CLD. Patients with other concomitant causes of liver disease, such as hepatitis B virus infection, autoimmune, alcohol abuse (>40 g/d of alcohol), or human immunodeficiency virus, were not included in the study. Moreover, patients who had been included in a previous study17 but who represent the same population (ie, reproductibility) and produces accurate predictions in a different but related population (ie, transportability).15

Thus, the aims of this study were as follows: (1) to assess the reproducibility and transportability of the AST/ALT ratio in a large cohort of patients with different degrees of CLD related to HCV infection alone, (2) to confirm the correlation between the progressive impairment of liver function and the increase in the AST/ALT ratio in these patients, (3) to evaluate whether the accuracy of the AST/ALT ratio in the noninvasive diagnosis of cirrhosis can be improved by using it with other variables, and (4) to estimate the 1-year prognostic ability of the AST/ALT ratio compared with the Child-Pugh and the MELD scores in patients with HCV-related cirrhosis.

The anti-HCV antibodies were detected by a third-generation enzyme immunoassay that contains HCV antigens from the viral core and from areas of the nonstructural NS5, NS4, and NS5 regions (Ortho HCV SAVe 3.0; Ortho-Clinical Diagnostics Inc, Raritan, NJ). Positivity for anti-HCV antibodies was confirmed by a strip immunoassay test (RIBA HCV 3.0; Chiron Corp, Emeryville, Calif). The HCV genotypes were determined by means of INNO-LiPA HCV II (Innogenetics Inc, Zwijndrecht, Belgium), which is a reverse hybridization-based test that uses specific probes immobilized in parallel lines on membrane strips and allows the determination of 6 HCV genotypes and their most common subtypes. Genotypes were classified according to the classification proposed by Simmonds.19

Diagnosis of chronic hepatitis was made histologically by means of percutaneous liver biopsy using the Menghini technique. The liver biopsy specimen was then fixed in formalin and embedded in paraffin and scored according to the methods described by Scheuer20 by a pathologist (P.C.) unaware of the patients’ clinical data. Fibrosis was considered separately from grading to avoid overlapping between staging and grading. Liver cirrhosis was diagnosed either histologically (n=4) or on the basis of clinical signs of portal hypertension, Doppler ultrasonographic measurements, and/or endoscopic presence of esophageal or gastric varices. However, the presence of thrombocytopenia was not considered a diagnostic criterion for cirrhosis to rule out possible confounding factors in subsequent analyses. Clinical severity of liver disease in cirrhotic patients was evaluated by means of the Child-Pugh score, calculated on the day of biochemical and functional evaluation.21

All patients had undergone monoethylglycinexylidide (MEGX) testing at the time of liver biopsy (chronic hepatitis) or clinical evaluation (cirrhosis), as previously described. Briefly, the MEGX test was performed as follows: lidocaine was administered at the dose of 1 mg/kg by slow (over 2 minutes) intravenous infusion. A blood sample was obtained 30 minutes after the end of the lidocaine infusion. The MEGX concentration at sampling time was calculated as follows: MEGX–MEGXx. The MEGX was measured using fluorescence polarization immunoassay with the TD-2 system (Abbott Laboratories, North Chicago, Ill).

Biochemical evaluation was performed at the same time as the MEGX test on the day of liver biopsy (chronic hepatitis) or clinical evaluation (cirrhosis). A blood sample for the assessment of AST, ALT, γ-glutamyltranspeptidase, alkaline phosphatase, total bilirubin, albumin, prothrombin activity (PA), and platelet count (PLT) was obtained from all patients after an overnight fast. The AST/ALT ratio was then calculated for each patient. We evaluated stability of the AST/ALT ratio monthly for 3 consecutive months in a group of 10 patients (5 chronic hepatitis patients without therapy and 5 cirrhotic patients) and weekly for 2 consecutive weeks in another group of 20 cirrhotic patients, which should represent a more unstable group. In both groups, the AST/ALT ratio was consistently less than 1 or 1 more in each patient, despite amino transferase fluctuations over time.

Sixty-three cirrhotic patients of the cohort of 252 patients were followed up for at least 1 year. In these patients, MELD scores were calculated on variables obtained at referral. The MELD score was calculated according to the original formula proposed by the Mayo Clinic group16:

\[
3.8 \times \log_b \left( \frac{Bilirubin}{[\text{mg/dL}]} \right) + 11.2 \times \log_b \left( \text{INR} \right) + 9.6 \times \log_b \left( \frac{Creatinine}{[\text{mg/dL}]} \right) + 6.4 \times \text{Etiology} \\
(0 \text{ if Cholestatic or Alcoholic, } 1 \text{ Otherwise}).
\]

Prothrombin expressed as percent activity was converted to prothrombin time INR (international normalized ratio) using internal standards of the laboratory.

Analysis of the patients’ characteristics was performed by considering 2 subgroups of patients (with AST/ALT ratios <1 or ≥1). Comparisons were performed using the Mann-Whitney U test. Analysis of variance was used in multiple comparisons. The χ² test was used to compare proportions. Correlations between the AST/ALT ratio and MEGX test, between PLT and MEGX test, and between AST/ALT ratio and MELD score were performed using the Spearman rank correlation test (rₛ). The patients’ biochemical (AST, ALT, AST/ALT, γ-glutamyltranspeptidase, alkaline phosphatase, total bilirubin, PA, PLT) and functional (MEGX values) variables were used in stepwise logistic multivariate regression analysis to identify variables independently associated with cirrhosis.

Receiver operating characteristic (ROC) curves were used to assess the PLT cutoff with the best sensitivity and specific-

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ity in the discrimination between cirrhotic and noncirrhotic patients and to assess the MELD scores and AST/ALT ratios with the best sensitivity and specificity in discriminating between cirrhotic patients who survived and those who died within 1 year of follow-up. Univariate survival curves were estimated using the Kaplan-Meier method with the AST/ALT ratio and MELD score cutoffs identified by means of ROC curves and compared using the log-rank test. Data are shown as mean ± SD. P < .05 for 2-sided tests was considered statistically significant. Statistical analysis was performed using the SPSS statistical package (SPSS Inc, Chicago, Ill).

**RESULTS**

The mean age of the patients was 48 ± 12 years. One hundred eighty-six patients were men (74%). Cirrhotic patients represented 36% of the population. The HCV genotype was 1a in 30, 1b in 113, 2a/c in 59, 3a in 38, 4 in 9, and mixed in 3 patients. **Table 1** presents the distribution of patients according to the AST/ALT ratio (<1 or ≥1) and different degrees of severity of disease (histologic staging and Child-Pugh classes). All chronic hepatitis patients without fibrosis had an AST/ALT ratio less than 1. The mean AST/ALT ratio in patients with cirrhosis was 1 or greater. Chronic hepatitis patients more frequently had AST/ALT ratios less than 1 compared with cirrhotic patients (chronic hepatitis, 159/166 [96%]; cirrhosis, 18/86 [21%]; χ² = 148.3; P < .001). Furthermore, a higher proportion of chronic hepatitis patients with low fibrosis scores (chronic hepatitis, 159/166 [96%]; cirrhosis, 18/86 [21%]; χ² = 148.3; P < .001) and of cirrhotic patients with compensated disease had AST/ALT ratios less than 1 (χ² = 10.0; P = .007). The mean Child-Pugh score was higher in patients with AST/ALT ratios of 1 or more (8.0 ± 1.9 vs 5.8 ± 1.2; P < .001, Mann-Whitney U test).

We observed a significant inverse correlation between the MEGX values and the AST/ALT ratio (n = 252) (r = −0.621; P < .001, Spearman rank correlation test). Moreover, MEGX values were significantly lower in patients with AST/ALT ratios of 1 or more compared with patients with AST/ALT ratios less than 1 (24.8 ± 23.2 vs 68.4 ± 28.9 ng/mL; P < .001, Mann-Whitney U test).

Patients with histologic findings of liver cirrhosis were grouped together with Child-Pugh class A patients. **Table 2** shows that the AST/ALT ratio progressively increased and MEGX values concomitantly decreased starting from patients without cirrhosis, through patients with cirrhosis, and up to patients with advanced liver disease (P < .001, analysis of variance). Moreover, the mean AST/ALT ratio of chronic hepatitis patients with fibrosis scores of 0 to 3 was significantly different from that of chronic hepatitis patients with fibrosis scores of 4 plus compensated cirrhotic patients (P < .001, Mann-Whitney U test), and the AST/ALT ratio of patients with compensated cirrhosis was significantly different from that of patients with uncompensated cirrhosis (P < .001, Mann-Whitney U test). Patients with less severe liver disease and less compromised liver function more frequently had AST/ALT ratios less than 1 (χ² = 162.0, P < .001).

Multivariate stepwise logistic analysis showed that AST/ALT ratio (odds ratio [OR] for a variation of 0.1, 1.503; 95% confidence interval [CI], 1.205-1.874), PLT (OR for a variation of 1000, 0.982; 95% CI, 0.971-0.994), MEGX values (OR for a unitary variation, 0.960; 95% CI, 0.933-0.988), and PA (OR for a unitary variation, 0.933; 95% CI, 0.881-0.988) in this order were independently associated with the presence of cirrhosis.

The ROC curve showed that a PLT cutoff of 130 × 10³/µL had the highest specificity (88.3%; 95% CI, 82.3-92.8) and sensitivity (91.1%; 95% CI, 83.2-96.1) in differentiating cirrhosis from noncirrhotic patients. Therefore, we evaluated whether the combination of an AST/ALT ratio cutoff of 1 and PLT cutoff of 130 × 10³/µL would improve the accuracy of noninvasive diagnosis of cirrhosis. **Table 3** shows specificity, sensitivity, PPV, and NPV of these variables alone or together. An AST/ALT ratio of 1 or higher incorrectly classified 5 patients as having cirrhosis, whereas it was not able to diagnose cirrhosis in 20 patients. Furthermore, the combined assessment of the AST/ALT ratio and PLT cutoffs classified 2 patients as having cirrhosis who actually did not, whereas the AST/ALT ratio or PLT incorrectly classified 3 patients with cirrhosis as not having cirrhosis. Since PPV and NPV were obtained considering the prevalence of cirrhosis observed in our study, we performed a computed...

**Table 1. Distribution of Patients According to the AST/ALT Ratio and Severity of Disease**

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>AST/ALT Ratio</th>
<th>n</th>
<th>AST/ALT Ratio</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis fibrosis score</td>
<td>0</td>
<td>57 (32)</td>
<td>1</td>
<td>53 (30)</td>
</tr>
<tr>
<td>1</td>
<td>26 (15)</td>
<td>2</td>
<td>21 (12)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (1)</td>
<td>3</td>
<td>23 (3)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis Child-Pugh class</td>
<td>A</td>
<td>17 (12)</td>
<td>B</td>
<td>21 (28)</td>
</tr>
<tr>
<td>6 (3)</td>
<td>28 (37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0</td>
<td>19 (25)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. AST/ALT Ratios and MEGX Values in Patients With Various Degrees of Disease Severity**

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>No. of Patients</th>
<th>AST/ALT Ratio</th>
<th>MEGX Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis fibrosis score 0-3</td>
<td>162</td>
<td>0.6 ± 0.2</td>
<td>71.8 ± 28.3</td>
</tr>
<tr>
<td>Chronic hepatitis fibrosis score 4, cirrhosis Child-Pugh class A</td>
<td>37</td>
<td>1.1 ± 0.4</td>
<td>33.0 ± 22.1</td>
</tr>
<tr>
<td>Cirrhosis Child-Pugh classes B and C</td>
<td>53</td>
<td>1.5 ± 0.5</td>
<td>23.7 ± 19.3</td>
</tr>
</tbody>
</table>

Abbreviations: AST/ALT, aspartate aminotransferase–alanine aminotransferase; MEGX, monoethylglycinexylidide.

*Data are presented as mean ± SD. Differences among groups are statistically significant (P < .001, analysis of variance).
simulation to evaluate the modifications in PPV and NPV using various prevalences of cirrhosis. Therefore, we applied 2 arbitrarily determined prevalences (30% and 40%) of cirrhosis, as well as those observed in previous studies that evaluated the AST/ALT ratio in patients with HCV-related CLD, to our results and recalculated the prevalence-adjusted PPV and NPV (Table 4).

Sixty-three of the 90 patients with cirrhosis were followed up for at least 1 year. Forty-six patients were men, and the mean age of the patients was 52±10 years. Twenty-one patients had Child-Pugh class A disease, 32 had class B disease, and 10 had class C disease.

During 1-year follow-up 16 patients died (2 patients with Child-Pugh class A disease, 10 with class B disease, and 4 with class C disease). All patients died of liver-related death. The AST/ALT ratios, Child-Pugh scores, and MELD scores were significantly higher among patients who died compared with those who survived (AST/ALT ratio, 1.5±0.5 vs 1.3±0.6; P=.02; MELD score, 8±4 vs 6±5; P=.05; Child-Pugh score, 8±2 vs 7±2; P=.02). The AST/ALT ratios showed significant correlation with both MELD (r = 0.596; P < .001) and Child-Pugh scores (r = 0.558; P < .001).

The ROC curves identified an AST/ALT ratio cutoff of 1.16 (sensitivity, 81.3%; 95% CI, 54.4-96.0; specificity, 55.3%; 95% CI, 41.1-69.8), a MELD score cutoff of 9 (sensitivity, 56.3%; 95% CI, 29.9-80.2; specificity, 74.5%; 95% CI, 58.3-86.2) as having the best sensitivity and specificity in predicting 1-year survival. The Figure shows the Kaplan-Meier survival curves of the patients according to AST/ALT ratio (Figure, A), MELD score (Figure, B), and Child-Pugh score (Figure, C) cutoffs identified by means of receiver operating characteristic curves.

CI, 59.7-86.1), and a Child-Pugh score cutoff of 7 (sensitivity, 75.0%; 95% CI, 47.6-92.6; specificity, 59.6%; 95% CI, 44.3-73.6) as having the best sensitivity and specificity in predicting 1-year survival. The Figure shows the Kaplan-Meier survival curves of the patients according to AST/ALT ratio (Figure, A), MELD score (Figure, B), and Child-Pugh score (Figure, C) cutoffs identified by means of ROC curves. Patients with an AST/ALT ratio greater than 1.16 (P = .02) and patients with a MELD score greater than 9 (P = .01) or a Child-Pugh score greater than 7 (P = .01) had significantly shorter survival.

COMMENT

More than a decade ago, Williams and Hoofnagle6 performed a retrospective study that demonstrated that in a population of patients with nonalcoholic liver disease,
an AST/ALT ratio of 1 or more strongly suggested the presence of cirrhosis. They even noted that the development of cirrhosis in chronic hepatitis patients who were longitudinally followed up was accompanied by an increase in the AST/ALT ratio of 1 or more. Since then, the AST/ALT ratio has been extensively evaluated, both alone and as a part of discriminant scores, to noninvasively assess the presence of cirrhosis in patients with CLD.\textsuperscript{5,6,10-17,23}

To date, chronic HCV infection is the most common cause of liver disease in Western countries\textsuperscript{2} and represents an important social and economic burden.\textsuperscript{8,9} Therefore, many researchers have been prompted to test the usefulness and diagnostic ability of a low-cost and readily available variable such as the AST/ALT ratio in patients with HCV-related CLD, although they have obtained conflicting results. Actually, the encouraging results obtained by Sheth et al\textsuperscript{5} were reproduced by some authors\textsuperscript{10,11,15} but not by all.\textsuperscript{13,14} Moreover, other important questions regarding the relationships between aminotransferase and liver status in patients with HCV-related CLD have been raised.\textsuperscript{24-29} Finally, the prognostic usefulness of this simple and objective variable has never been tested, even though the future trends in prognostic assessment of cirrhotic patients seem to rely on simplicity and reproducibility.\textsuperscript{18,30}

In this debate, we suggest that the AST/ALT ratio warrants more extensive evaluation. In fact, since both aminotransferases are usually determined and are part of the common diagnostic workup of patients with liver disease, we think that the information obtained should be used to its fullest extent. Furthermore, we believe that the use of a ratio bypasses the problems related to the interpretation of different aminotransferase cutoffs. In addition, we believe that the common assumption of liver function tests as surrogates for histologic analysis or clinical evaluation should be overcome. Rather, they should be considered useful tools that can provide complementary and not mutually exclusive information to improve patient care. Therefore, in this retrospective study performed on a large cohort of patients infected with HCV and with varying degrees of CLD, our aims were to assess the reproducibility and transportability of the AST/ALT ratio in patients with single-origin liver disease, to confirm its relationship with liver function, to evaluate whether its diagnostic accuracy can be improved by associating it with other simple and commonly obtained variables, and to estimate its prognostic ability in patients with HCV-related cirrhosis.

Our study confirmed the results that Sheth et al\textsuperscript{5} and we\textsuperscript{13,17} previously obtained, thus demonstrating transportability and reproducibility of the AST/ALT ratio. The AST/ALT ratio significantly discriminated between chronic hepatitis patients and patients with compensated cirrhosis, 2 entities that can be hard to differentiate on conventional clinical basis. Moreover, the AST/ALT ratio was significantly different between patients with compensated vs noncompensated cirrhosis, therefore allowing grading of the disease.

In this study, an AST/ALT ratio of 1 or more misclassified only 7% (95% CI, 2.2%-14.9%) of the patients as having cirrhosis, whereas this variable did not diagnose cirrhosis in 11% (95% CI, 7.0%-16.9%) of the patients who actually had cirrhosis. Moreover, the AST/ALT ratio proved to be reproducible, since the results we previously obtained in an independent cohort of patients with CLD of various origins were confirmed in the present study. Finally, the presence of a correlation between progressive liver functional impairment and an increase in the AST/ALT ratio was confirmed even in this study, which was performed on a distinct population of patients with CLD.

Multivariate analysis identified AST/ALT ratio, PLT, MEGX values, and PA as variables independently associated with the presence of cirrhosis. All these variables, with the exception of MEGX values, are part of the common diagnostic workup of patients with liver disease and are frequently used to monitor the evolution of CLD. However, when classifying patients we did not consider thrombocytopenia as a diagnostic criterion for cirrhosis to rule out possible confounding factors in subsequent analyses. A PLT cutoff with the best sensitivity and specificity in differentiating cirrhotic patients from noncirrhotic patients was identified by means of ROC curve and then combined with the AST/ALT ratio to verify whether the noninvasive diagnostic accuracy of the AST/ALT ratio could be improved. The combined assessment of these variables was not able to diagnose cirrhosis in 2% of the patients, whereas it diagnosed 3% of the noncirrhotic patients as having cirrhosis. However, as previously emphasized,\textsuperscript{13} these results should be analyzed by evaluating the prevalence of the disease in the population. Therefore, we performed a simulated analysis by adjusting the PPV and NPV we obtained in this study (prevalence of cirrhosis, 36%) to 2 arbitrarily determined prevalences and to the ones observed in previous studies regarding the AST/ALT ratio in anti-HCV–positive patients (Table 4). The AST/ALT ratio and PLT showed PPV and NPV overall above 95%, although this kind of simulated analysis may have some limits, such as the use of different diagnostic criteria for diagnosis of cirrhosis among studies and the fact that some studies were performed only in patients with compensated disease.

The results of our study were surprisingly in keeping with those previously obtained in different populations in other countries. In fact, AST/ALT ratio, PLT, and PA were part of a “cirrhosis discriminant score” for the diagnosis of cirrhosis that was identified by means of a stepwise discriminant analysis in a US population of patients with nonalcoholic CLD.\textsuperscript{31} Moreover, the utility of combining these 3 variables in the noninvasive diagnosis of cirrhosis was further supported by a study conducted by Bonacini et al\textsuperscript{32} on a US population of patients with anti-HCV–positive CLD, although their results have recently been questioned.\textsuperscript{33} In addition, the predictive power of PLT in patients with cirrhosis has previously been emphasized. In fact, regression analyses identified low PLT as a variable independently correlated with survival,\textsuperscript{33} and PLT cutoffs were useful as clinical predictors of the presence of any varices and large esophageal varices.\textsuperscript{34}

One of the major criticisms regarding the AST/ALT ratio is its lack of prognostic utility. However, its prognostic accuracy has never been tested to our knowledge.
following the study by Williams and Hoofnagle.\(^7\) Prognostic use of the AST/ALT ratio in patients with chronic hepatitis would be unfeasible, since modifications of the ratio over time in this subset of patients might take a long period and most chronic hepatitis patients undergo antiviral treatment, hence modifying to some extent the course of the disease. We prospectively evaluated the possible use of the ratio focusing on the medium-term (1-year) prognostic assessment of patients with HCV-related cirrhosis. Therefore, we evaluated the prognostic yield of the AST/ALT ratio and compared its performance with that of definite prognostic tools, such as the MELD and Child-Pugh scores. We observed that the medium-term cirrhotic patients who died had higher mean AST/ALT ratios and higher MELD and Child-Pugh scores compared with patients who survived. Moreover, AST/ALT ratios were significantly correlated with both MELD and Child-Pugh scores. We initially showed that a simple and reproducible variable such as the AST/ALT ratio has prognostic value in predicting 1-year mortality of patients with HCV-related cirrhosis and that its prognostic accuracy is no different from that of established prognostic scores such as the MELD and Child-Pugh scores. Since we even showed that the AST/ALT ratio was able to grade the disease in patients with cirrhosis, being significantly higher in patients with noncompensated compared with well-compensated disease, it would be interesting to evaluate the prognostic meaning of AST/ALT modifications over time.

Although many studies were performed evaluating the AST/ALT ratio in CLD, most did not provide an explanation for the increase in the ratio as liver disease worsens, and the reason for this finding is still not clear. ALT is localized solely in the cellular cytoplasm, whereas AST is both cytosolic and mitochondrial. The half-life is approximately 47 hours in the circulation of ALT, approximately 17 hours for total AST, and on the average of 87 hours for mitochondrial AST.\(^35\) Clearance of AST is primarily performed within the liver by sinusoidal cells.\(^36,37\) In this study, we confirmed the presence of a close correlation between the AST/ALT ratio and a variable of liver function, which evaluates the hepatocellular functioning mass and partly depends on liver blood flow (MEGX test). Therefore, these findings seem to suggest that both shunting of functional liver blood flow and progressive damage to mitochondrial structures may be responsible for the increase in the AST/ALT ratio as liver disease worsens.\(^17\)

Nonetheless, our study has some drawbacks that need to be discussed. First, it is retrospective; second, AST levels can increase for conditions independent of liver disease (eg, muscle trauma); third, assessment of PLT in patients with HCV-related liver diseases should be carefully evaluated since factors other than portal hypertension may account for low PLTs. However, regarding the first point, we believe that on the basis of the availability of effective therapy no prospective study of this kind could be performed to evaluate the natural history of untreated patients due to ethical reasons. Moreover, conditions leading to nonhepatic AST elevation can be easily ruled out by simple clinical and biochemical workup. Finally, although thrombocytopenia may be related to mechanisms other than hypersplenism, these seem to be linked to advanced disease and deranged liver function. In fact, decreased thrombopoietin production seems to be an important determinant of this hematologic abnormality in CLD, whereas autoimmune thrombocytopenia and myelosuppression by HCV are not frequent events.\(^38\) The amount of thrombopoietin production strictly depends on liver functional mass.\(^39\) The relationship we observed between MEGX values and PLT (n=252) (\(r_s=0.540; P<0.001\), Spearman rank correlation test) seems to fit well with this hypothesis.

**CONCLUSIONS**

We suggest that the AST/ALT ratio should be placed in the right position within the workup of patients with CLD of various origins. In fact, although we are well aware that liver biopsy in patients with chronic hepatitis and Child-Pugh score in patients with cirrhosis are considered the gold standard for assessing disease severity due to their diagnostic and prognostic value, we are also aware that these evaluations have some drawbacks.\(^30,32,40\) In fact, not all patients can or want to undergo liver biopsy to stage the disease, and in clinical practice repeating this procedure simply to follow up the evolution of the disease over time is not propasable to patients who cannot be treated or who have not responded to antiviral treatment. In addition, the Child-Pugh score has some drawbacks, such as subjectivity of clinical variables and limited discriminant ability.

Therefore, we suggest that the AST/ALT ratio determination could be useful in well-defined clinical situations due to its relationships with stage of disease (both histologic and clinical) and its correlation with liver function. Diagnostically it may help the clinician assess patients who cannot or do not want to undergo liver biopsy, whereas from a prognostic point of view, it may help in following up patients who are not suitable for or who have not responded to antiviral therapy, thus avoiding the need for additional liver biopsies. Finally, the AST/ALT ratio seems to be a useful tool even in patients with cirrhosis, since it helps grade the disease and is correlated with 1-year prognosis.

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