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Letter to the Editor

From the CUPIC study: Great times are not coming (?)

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From the CUPIC study: Great times are not coming (?)

To the editor:

We read with interest the article by Hézode et al. in which they describe the week 16 interim results from the CUPIC study, a large French multicenter prospective cohort study [1]. Given the strict inclusion criteria of protease inhibitors (PI) phase III trials, the cirrhotic group was underrepresented and composed of highly selected patients in these studies [2–5]. Therefore, efficacy and safety concerns about first-generation PI-based therapy in “real-life” cirrhotic patients were raised. The CUPIC investigators found that albumin levels <35 g/L and platelet count ≤100,000/mm³ were independent predictors of death and severe complications, and the risk of these events in patients with both predictors was worryingly high (44.1%). The findings from the CUPIC study, important as they are, need to be qualified given two important caveats that we would like to discuss.

First, as the authors mentioned in the methods section, the safety interim analysis was not pre-specified in the original protocol and the sample size was not estimated for this purpose. As a result, the study was probably underpowered to investigate factors associated with such a low incidence event (death or severe complications). This issue is even more relevant when we analyze the number of variables included in the multivariate analysis presented in Table 3. It is generally recommended that a minimum of 10 events per variable should be used in logistic regression models, since increasing bias and variability, unreliable confidence interval coverage, and problems with model convergence emerge as the events per variable ratio declines below 10 and especially below five [6,7]. In the article by Hézode and colleagues, the multivariate analysis included 12 variables found to be associated with death or severe complications in univariate analysis, whereas only 29 events occurred (2.4 events per variable included). The adequate interpretation of the model is further hampered by the probable
significant multicollinearity between several independent variables included, like bilirubin, albumin, Child-Pugh score and MELD score.

Based on the figures shown on the article’s Table 4, we have calculated the accuracy parameters for albumin levels <35 g/L and platelet count ≤100,000/mm³, either alone or in combination, for the prediction of death or severe complications (Table 1). Albumin exhibited higher specificity as compared to platelet count (89% vs. 79%), with comparable sensitivity (57% vs. 60%). Moreover, the positive likelihood ratio (LR+) was much higher for low albumin levels than low platelet count (5.02 vs. 2.82). When both parameters were used in combination, there was a modest gain in specificity (95%) and a significant increase in LR+ (10.50). Given that the LR+ tells us how much to increase the probability of event if the test is positive, these results indicate that a serum albumin level <35 g/L can indeed be regarded as a good predictor of death and severe complications in cirrhotic patients treated with first-generation PI-based regimens, particularly when associated with a platelet count ≤100,000/mm³. Interestingly, the negative predictive value was high (>95%) for all parameters, which can prove to be a reassuring finding and a valuable tool if confirmed in other cohorts.

In conclusion, although we acknowledge the unquestionable importance of the CUPIC study, we believe that its results do not support the author’s definitive conclusion that treatment-experienced cirrhotic patients with platelet count and albumin levels below the mentioned cutoffs should not be treated with telaprevir or boceprevir. Conceivably, additional studies will be able to confirm CUPIC’s findings, or will even propose alternative strategies for high risk patients, like antibiotic prophylaxis or low accelerating dose regimen for interferon. Until then, we believe that triple therapy should not be denied to patients who do not meet the proposed albumin/platelet criteria, but rather they should be treated in specialized centers with liver transplant programs, by experienced hepatologists. The current approved PI-based regimen will probably be the standard-of-care for HCV patients for many years in several countries and,
even though IFN-free regimens are coming, it may be a very distant reality for many cirrhotic patients at risk for decompensation in the near future.

**Conflict of interest**

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

**References**


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Table 1. Performance of albumin levels and platelet count alone and in combination as predictors of death or severe complications according to the CUPIC Study data.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 429)</th>
<th>Death or severe complications</th>
<th>Accuracy (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>No (n = 400)</td>
<td>Yes (n = 29)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Albumin (n = 74)</td>
<td>≥ 35</td>
<td>367</td>
<td>354</td>
<td>13</td>
<td>87</td>
<td>57</td>
<td>89</td>
<td>27</td>
<td>97</td>
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<tr>
<td></td>
<td>&lt; 35</td>
<td>62</td>
<td>45</td>
<td>17</td>
<td></td>
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<tr>
<td>Platelet count (n = 129)</td>
<td>&gt; 100,000</td>
<td>326</td>
<td>314</td>
<td>12</td>
<td>77</td>
<td>60</td>
<td>79</td>
<td>19</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>≤ 100,000</td>
<td>103</td>
<td>85</td>
<td>18</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Albumin &lt; 35 g/L AND</td>
<td>No</td>
<td>395</td>
<td>380</td>
<td>15</td>
<td>92</td>
<td>50</td>
<td>95</td>
<td>44</td>
<td>96</td>
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<tr>
<td>Platelet count ≤</td>
<td>Yes</td>
<td>34</td>
<td>19</td>
<td>15</td>
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<td>100,000/mm³</td>
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NOTE. PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.