increased number of false positives. Where Olesen and colleagues see reasons for concern, we see two separate sets of interesting data leading to the same conclusion. In science, this is always of great comfort.

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.

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Effect of abstinence on the prognosis of patients with alcoholic liver disease: A word of caution

To the Editor:

We read the article by Lackner and collaborators [1] with great interest. The main goal of this study was to assess factors associated with long-term prognosis in patients with biopsy-proven alcoholic liver disease (ALD). Although this study is of major clinical relevance, we believe it deserves several comments.

The authors concluded that alcohol abstinence determines the long-term prognosis of patients with ALD. However, this statement is not supported by the study results because abstinence was not associated with improved survival in multivariate analysis. As this study included a limited number of patients, the lack of significance may be related to false negative results. In addition, the authors choose to perform separate analyses in patients with early/compensated and decompensated ALD, which further increased the risk of type II error, especially in the group of patients with compensated ALD which comprised of only 60 patients. Furthermore, the authors also chose to include all variables that reached a p value <0.20 in univariate analyses, in the multivariate model. As a result, a significant number of variables were taken into account in these analyses. Considering that only 13% of the patients with compensated ALD had died from liver-related complications at 5 years, only a couple variables should have been included in the Cox regression analysis. Unfortunately, a power calculation was not available. Finally, non-significant results of the univariate analyses as well as the results of all multivariate analyses were not provided. Hence, the reader does not have access to many relevant data allowing for an accurate interpretation of the study results. In studies like this one, a large number of patients, followed for a long period of time are required to ensure that enough events occur. Thus, the statistical analyses performed in both compensated and decompensated patients should have been of interest to assess the impact of abstinence on patient prognosis in the whole study population.

Another matter of debate concerns the statistical approach used in this study. While we acknowledge that liver-related causes accounted for most of the deaths in patients with cirrhosis related to ALD, not taking into account other causes of deaths would have require the use of appropriate models of disease progression. It is unclear why authors used a Cox regression analysis rather than competing risk analysis, as recommended [2]. Hence, even if the study of Lackner and collaborators brought some useful data, many drawbacks limit the interpretation of their results. Further prospective studies using appropriate models for disease progression and including large series of ALD patients are required.

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Reply to: "Effect of abstinence on the prognosis of patients with alcoholic liver disease: A word of caution"

To the Editor:

We thank Deltenre *et al.* [1] for their interest in our study on long-term prognosis in patients with alcoholic liver disease (ALD) [2]. In response to their methodological concerns, we would like to clarify the following points:

The main finding of our study was the impact of histological features, in particular fibrosis type and stage, on long-term prognosis in ALD. We also found a benefit of alcohol abstinence during follow-up as abstinent patients showed significantly better survival on Kaplan-Meier analysis both in early/compensated and decompensated ALD. Thus, our data are consistent with previous findings on the benefit of abstinence in advanced ALD and suggest a similar benefit in early stages of ALD where large longitudinal studies are lacking to date [3,4]. With respect to Cox regression, the results of univariate analyses for all tested variables are displayed online under Supplementary data. Abstinence was a significant variable on univariate analysis in early/compensated ALD ($p = 0.044$, Supplementary Table 1) as well as in decompensated ALD ($p = 0.016$, Supplementary Table 4) but not on multivariate analysis in these groups. However, in the subgroup of patients with histological alcoholic steatohepatitis (ASH), abstinence proved to be an independent predictor of survival on multivariate Cox regression ($p = 0.007$, see Supplementary Table 6).

It is important to emphasize that there is overwhelming evidence that cessation of the cause of liver disease (*e.g.* viral hepatitis clearance) is associated with recompensation of the liver disease and/or some degree of fibrosis reversibility, positively impacting patients' outcome [5,6]. In the field of ALD, there is a clear lack of studies assessing the role of abstinence as well as clinical trials testing new strategies to promote permanent alcohol cessation. Although we agree that this study has some limitations, we think that the results are robust enough to raise awareness on the importance to treat alcohol use disorder in patients with ALD.

As suggested by Jepsen *et al.* [7] cirrhosis could be viewed as a multistate disease model. In this setting, factors contributing to disease progression should be estimated by competing risk analysis. Interestingly, Jepsen *et al.* recently demonstrated that comorbid diseases contribute only little to overall mortality in alcoholic cirrhosis [8]. However, it was not our aim to investigate the outcome of alcoholic cirrhosis, which was not present in all patients in our study. This was particularly true in early/compensated ALD patients, among whom 60% did not have cirrhosis on histology. We believe that in clinical practice, ALD is not encountered as a continuum (with an equal distribution of the whole spectrum of the disease) but rather as two distinct clinical settings, *i.e.* early/compensated ALD (usually outpatients that may or may not seek medical care) *vs.* decompensated ALD (usually inpatients that are hospitalized due to complications of cirrhosis). Using this distinct approach, we investigated the association between risk factors and liver-related death in each group. Cox regression analysis to directly quantify the hazard ratios among those individuals who are actually at risk of developing the event of interest (cause-specific effect size), may be more appropriate for this research question than using the sub-distribution hazards method (Fine and Gray model) [9,10].

We decided to include variables with a p value <0.2 on univariate analysis into multivariate Cox regression in order not to miss important variables. We are well aware of the limited robustness of our model considering the ratio of variables to events, especially in the early/compensated group given the relatively low number of patients. This fact was also referred to in the