Do fatigue and UDCA therapy truly have independent effects on mortality in PBC?

To the Editor:
We read with interest the paper by Jones et al. [1] regarding the impact of fatigue and ursodeoxycholic acid (UDCA) treatment on mortality in PBC. The authors are to be congratulated on their accrual and close follow up of a well characterised group of patients and their efforts have certainly expanded further our understanding of the natural history and the effects of pharmacological interventions in PBC.

Nonetheless, caution must be exercised when evaluating their dataset and conclusions, particularly in respect of the independent effect of fatigue and UDCA usage on mortality for the following reasons.

Firstly, whilst on univariate analysis both the presence of fatigue (which, importantly was identified here as a categorical variable) and lack of use of UDCA were associated with increased mortality, only 43 deaths were recorded. Consequently, the analysis of seven different variables in the Cox regression model is possibly excessive and could lead to statistical errors in its output as the “rule of thumb” of regression analysis has historically been a minimum of 10 outcome events per variable. However, recent reports suggesting the use of 5–9 outcomes per variable only uncommonly lead to statistical error, though is slightly more common with Cox models [2].

Secondly, fatigue, previously identified as categorical (present or absent), is now interpreted as a linear score (based on the FIS) as part of the Cox model. Therefore, although a 1 point increase in the FIS is independently associated with an increased mortality (risk ratio 1.008), how the presence (or otherwise) of fatigue affects mortality in an independent model is not certain.

Thirdly, and perhaps most crucially, in this model, UDCA therapy was not independently predictive of improved mortality at all with a risk ratio of 0.728 (95% CI 0.370–1.432) p = 0.357. This issue is of fundamental importance as it is at variance with the very title of the manuscript.

On a final note, the results in Table 1 suggests a possible typographical error in regard to the effect of age on mortality. The initial B value would suggest an increased risk for age and, therefore, a risk ratio of >1, especially given the highly significant p value. However, the risk ratio of 0.728% and 95% CI of 0.37–1.432 cannot provide such a highly significant p value, given the 95% CI clearly crosses 1.

In summary, whilst it remains possible that fatigue is independently associated with increased mortality in PBC, the data presented by Jones et al. in its published format does not prove that this is the case in respect of the presence or otherwise of fatigue. Furthermore, the use of UDCA therapy cannot be said to have any independent effect on mortality, based on the published data.

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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Reply to: Do fatigue and UDCA therapy truly have independent effects on mortality in PBC?

To the Editor:
We thank Drs. Yousuf and Yeoman for their appreciation of our work and interest in our recent paper [1] regarding the impact of fatigue and ursodeoxycholic acid (UDCA) treatment on mortality in PBC. Although they raise some interesting points, we believe they may not fully understand the conclusions we made in our paper. This is the largest series of patients with PBC followed up for a considerable period of time, and this cohort has provided important insights into the true impact that fatigue has on not only quality of life but also length of life.

Yousuf and Yeoman are correct, COX models can theoretically be limited in their interpretation as the number of variables is increased. If we had used this as our only analysis, we may have agreed with them; however, combined with the Kaplan Meier and Log Rank Test Analysis, which confirm the relationship between fatigue and mortality, we believe this enhances the