JOURNAL
OF HEPATOLOGY

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Reply to: "Individual surveillance using model-based hepatocellular carcinoma risk estimates in chronic hepatitis C patients after antiviral treatment"

To the Editor:

We are grateful for the very thoughtful comments and for the interest of Ji *et al.* in our work.

Ji *et al.* bring up the issue of incorporating the changes in characteristics after antiviral treatment into the prediction of hepatocellular carcinoma (HCC) risk. This issue is more complicated than it sounds because we need to consider time in the calculation. For example, over the next 5 years after antiviral treatment the platelet count may slowly/quickly increase, slowly/quickly decrease or stay the same and it may start from a high, low or normal starting point. Also, the more time a patient accrues cancer-free after antiviral treatment, the lower the subsequent risk (*i.e.* the risk at year 5 is likely to be lower than the risk at year 1). We are currently working on such longitudinal models of HCC risk prediction after antiviral treatment using multiple complementary statistical approaches.

Ji *et al.* recommend incorporating the level of decompensated cirrhosis and stage of fibrosis into the predictive models. We already evaluated clinical and laboratory characteristics of decompensated cirrhosis (ascites, varices, encephalopathy, bilirubin, albumin, international normalized ratio) for inclusion into the models that we published, of which only albumin made it into the final models. The stage of fibrosis would be a useful predictor (for example, estimated by elastrography) if it was available in a large proportion of patients.

Ji *et al.* question whether our models are generalizable to other populations. Clearly, it is very useful for a model to be tested and validated in additional populations – we are in the process of doing that and welcome any other opportunities for external validation! However, just because a population is different does not necessarily mean that the predictors of HCC in that population will be different. For example, a low platelet count may be associated with a 2-fold increase in HCC risk in our population, and would also be expected to be associated with a similar approximately 2-fold increase in HCC risk in a population that is predominantly Asian or a population that is predominantly female (unless a low platelet count means something completely different in Asians *vs.* Caucasians or in men *vs.* women). The absolute risk of HCC may be different in different populations but that would not be a problem if the difference is explained by differences in the prevalence of characteristics that are already included in the model. For example, a population that is predominantly female or has a lower mean age than our population would have a lower HCC incidence, but our model might still estimate HCC well because it includes sex and age as predictors.

Financial support

The study was funded by a NIH/NCI grant R01CA196692 and VA CSR&D grant I01CX001156 to GNI. The funding source played no role in study design, collection, analysis or interpretation of data.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.09.026.

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Hip fracture risk in patients with alcoholic cirrhosis: Do comorbidities and complications matter?

To the Editor:

Patients with liver disease are particularly susceptible to osteoporosis, making them prone to bone fractures.[1,2] The 30-day mortality rate in patients with bone fractures was approximately 6.7% according to the data collected from the National Hip Fracture Database.[3] Moreover, cirrhosis following hip fracture was associated with higher 30-day in-hospital mortality.[4] Nevertheless, the absolute risk of hip fractures in individuals with alcoholic cirrhosis is still unclear.

Recently, we read with great interest the study by Otete *et al.*[5] Using the Clinical Practice Research Datalink, Hospital Episodes Statistics, and National Patient Registry database, this population-based study of a large sample suggested that patients with alcoholic cirrhosis had a significantly higher risk of hip fracture and post-hip fracture mortality compared to the general population. The research appears informative clinically. Thus, we addressed some issues regarding this study.

Firstly, the incidence rate of diabetes mellitus increased all over the world.[6] Additionally, nearly 30% of cirrhosis patients have diabetes mellitus.[7] Theoretically, patients with liver cirrhosis had a higher incidence of bone fracture compared to those without diabetes mellitus.[8] Additionally, hypoglycemic treatment could modulate the risk of fractures.[9] Accordingly, it is essential to consider concurrent diabetes mellitus as a risk factor when analyzing the incidence rate of hip fracture in patients with alcoholic liver cirrhosis. Otete *et al.* did not report the information on concurrent diabetes mellitus.[5] Can the authors provide the relevant data?

Secondly, we are confused about the detection method for the diagnosis of liver cirrhosis. Theoretically, the symptoms and signs would not be apparent in the early phase of liver cirrhosis. Many patients with early stage liver cirrhosis would have missed diagnosis without routine and detailed inspection. Patients with early stage cirrhosis had a lower risk of bone fracture than those with late stage cirrhosis. If the patients with early stage cirrhosis are included in the alcoholic cirrhosis group, the absolute rate of fracture risk may decrease. Therefore, the results would be inaccurate without knowledge of how many patients had early stage liver cirrhosis.

Thirdly, the Charlson comorbidity score was not balanced between the cirrhosis and control group in the UK database. More patients had zero scores in the control group, which suggested that the disease burden in the control group was lighter than in the alcoholic liver cirrhosis group. Therefore, the results may be inaccurate without knowledge of the balance of demographic characteristics.

Fourthly, surgery was the primary therapy for patients with hip fracture. Evidence showed that early surgery reduced the overall mortality compared with control therapy.[10] However, Otete *et al.* did not illustrate the relevant details.[5] Additionally, the surgery-associated complications that relate to prognosis are also critical when assessing the absolute rate of post-hip fracture mortality.

In summary, we suggest that comorbidities and complications in alcoholic liver cirrhosis should be considered when analyzing the risk of hip fracture and post-hip fracture mortality. Clarification regarding these issues would significantly solidify the conclusions of the study by Otete *et al.*[5]

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Dr Ling-Yue Zhao and Yi-Jun Luo: Design of the work and final approval of the manuscript for submission. Dr Ling-Yue Zhao: Drafting and revision of the manuscript. Dr Jing Zhu: Revision of the manuscript. Dr Hong-Yue Liu: Revision of the manuscript.