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Authors' contributions

Data collection and statistical analyses: OM; patient follow-up: OM, ADB, LE, ALH, LL, OC, DR and NK; virological work-up: SL, FA and JI; paper preparation and review: OM, SL, FA, JI and NK; study design: NK.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.09.011.

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

To the Editor:

We read with interest the article by Ioannou and colleagues in which they discussed using a risk-based model to estimate the risk of hepatocellular carcinoma (HCC) after antiviral treatment for hepatitis C virus (HCV) infection.[1] A shortened surveillance interval (6-month *vs.* 3-month) after sustained virologic response (SVR) has been suggested in order to diagnose HCC-related tumors at a lower stage and a smaller size, allowing for curative treatment which improves survival and reduces recurrence rates after treatment of HCC.[2]

However, the cost-effectiveness of frequent HCC surveillance for individuals after antiviral treatment remains unclear, particularly during the era of direct-acting antiviral therapy when the number of HCV-infected patients who achieve SVR has increased dramatically. Therefore, it is very important to accurately stratify the risks of HCC development in patients who received antiviral treatments using a simple and noninvasive method to guide individualized monitoring. In this article, Ioannou and colleagues have performed an excellent study using data obtained from a US cohort of the Veterans Affairs

Health Care System to develop and internally validate 4 models to predict HCC following antiviral treatment based on cirrhosis and SVR status.[1] Their study showed that using model-based HCC risk estimates to determine whether to recommend screening/surveillance or not demonstrated a higher net benefit compared to the screen-all or screen-none strategies recommended by current HCC guidelines.[3] These models are very important and will potentially help clinicians to customize HCC surveillance strategies in individual patients; however, the risk of HCC is complex and requires additional considerations.

Firstly, to predict HCC in patients after antiviral treatment, the use of post-treatment laboratory measurements would be better than using pre-treatment measurements. This point has been discussed in previous studies which showed that post-treatment aspartate aminotransferase-to-platelet ratio index (APRI) and alpha-fetoprotein (AFP) better reflected the actual liver diseases status and risk of HCC development.[4,5] Thus, we suggest that post-treatment AFP and APRI levels are more reliable surrogate markers to predict HCC.[4–6]

Secondly, the authors suggested risk-based HCC surveillance among patients even without cirrhosis who had additional "adverse characteristics". We agree with the authors recommendation of using age as a variable for a surveillance decision, since older age is one of the risk factors of HCC development.[1,4,7] However, HCV-infected individuals without cirrhosis had a much lower HCC risk, especially in the younger patients.[8] In the model for no cirrhosis/no SVR subgroup, the high estimated risk of HCC may be attributable to pre-treatment parameters (low platelets and high aspartate/alanine aminotransferase levels), which can change significantly with treatment and thus post-treatment parameters should also be evaluated.

Thirdly, decompensated cirrhosis and the severity of liver fibrosis have been suggested to confer a significantly higher risk of HCC.[4,7,9] Therefore, the model may have a higher clinical impact by integrating hepatic decompensation and/or lever of fibrosis into the model, such that a recommendation may be available wherein the individual HCC surveillance interval can also be based on the severity of liver fibrosis and decompensated cirrhosis.

Finally, the resulting web-based tools may not be generalized to other populations (other races/ethnicities and female sex) without further validation. The model was derived mostly from older, predominantly male (96.6%), white (55.9%) and genotype 1 (79.2%) patients. This statement is particularly important when considering the following factors: i) more than half of the patients with chronic hepatitis C (CHC) in the world are from Asia and genotype 3 is the dominant genotype in Southeast Asia. Both Asian ethnicity and genotype 3 are independently associated with higher risk of advanced liver diseases and HCC risk,[6,10] ii) female sex is a protective factor in the progression of liver disease and HCC risk. The proportion of females in this database may limit the accuracy of predicting HCC in females. Therefore, we do suggest that this should have been noted as a limitation of the model.

In summary, the models of HCC risk estimated by Ioannou *et al*. enable clinicians to provide more individualized surveillance recommendations. Given the need for cost-effective post-SVR monitoring, validation studies from a more diverse population are warranted and future studies may also consider relevant post-SVR factors, hepatic decompensation, and the severity of liver fibrosis. However, this model does provide the framework for other clinicians to build from using the aforementioned factors, so these authors are to be congratulated for taking the first step in this fast-evolving field of treating patients with HCV.

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Conflicts of interest

Yee Hui Yeo, Caini He, Jie Li, Xuesong Gao, Zongfang Li, Linda Henry: have nothing to disclose. Fanpu Ji: Speaker's bureau: Ascletis and Gilead Sciences. Mindie Nguyen: Grant/research support: Gilead Sciences, Janssen; Advisory board member or consultant: Gilead Sciences, Janssen.

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

Supplementary data

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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.

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Conflict of interest

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

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