Risk score for development of HCC: ready for use in practice?

Surveillance is widely accepted in clinical practice in patients who are at increased risk of developing hepatocellular carcinoma (HCC), including those with chronic hepatitis B virus (HBV) infection. Surveillance in patients with HBV infection has been recommended on the basis of findings from one randomised controlled trial from China showing a survival benefit,¹ and other non-randomised or observational studies showing that surveillance detects earlier disease and improves survival. The most recent update of practice guidelines from the American Association for the Study of Liver Diseases (AASLD) recommends surveillance for HCC in Asian male hepatitis B carriers older than 40 years, Asian female hepatitis B carriers older than 50 years, hepatitis B carriers with a family history of HCC, African and North American black patients with hepatitis B, and hepatitis B carriers with cirrhosis.²

One of the main elements of surveillance is to establish what level of risk for HCC should lead to initiation of surveillance. In this issue of The Lancet Oncology, Hwai-I Yang and colleagues³ report the development and validation of a predictive score for the risk of development

often as recommended by the manufacturer, and simply report results as positive or negative. This approach downgrades hard-won quantitative data into simple qualitative testing; effort is needed to address how to use numerical faecal haemoglobin concentrations to improve screening programme performance in the future.

Much is known about outcomes for participants with positive FIT results; however, there are few reports on subsequent development of colorectal neoplasia in participants with initially negative results. In this issue of The Lancet Oncology, Chen and colleagues⁴ explore baseline faecal haemoglobin concentration as a predictor of incident colorectal neoplasia. 44 324 participants with negative findings at the first screen were followed up to find cases of colorectal neoplasia, and the association between baseline faecal haemoglobin concentration and risk of neoplasia was investigated. In participants with negative results, baseline haemoglobin concentration was predictive of the risk of adenoma and subsequent progression to cancer.

It is already well documented that faecal haemoglobin concentrations are related to disease, with values increasing from normal, through low-risk to high-risk adenoma to cancer, although there is overlap between these groups. Chen and colleagues⁴ extended this knowledge, showing that baseline faecal haemoglobin was related to outcomes over time at lower haemoglobin concentrations. Taking these data together, there is likely a continuum of risk of colorectal neoplasia as faecal haemoglobin increases from zero.

Chen and colleagues’ study⁴ provides implications for the design of screening programmes. Faecal haemoglobin concentration at baseline could provide a means for determining risk; low, intermediate, high-risk, and extremely high-risk groups could be defined, which would allow for individually tailored screening strategies, as discussed by the authors. With modern information technology, flair, and imagination, risk-adapted strategies could be adopted in future screening programmes. New data on associations between faecal haemoglobin concentration and demographic characteristics should also affect programme design. Colorectal cancer screening using faecal tests has become much less straightforward.

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I have received payment for consultancy work from Immunosystems Inc and Alpha Labs Ltd.

of HCC in patients with chronic hepatitis B. Although other groups, such as Yuen and colleagues,\(^4\) have reported risk scores for the development of this disease, this is the first group to provide validation of their risk score. The study analysed data from 3584 patients from a community-based Taiwanese cohort who were not receiving antiviral therapy and did not have cirrhosis, and validated their risk score in hospital-based cohorts from Hong Kong and South Korea.\(^1\) Variables associated with an increased risk of HCC included patient factors (male sex, increasing age), disease factors (raised concentrations of serum alanine aminotransferase), and virological factors (HBeAg positivity and increased levels of serum HBV DNA). The risk score accurately estimated the risk of development of HCC at 3, 5, and 10 years. The investigators have contributed to the evolving work into risk scores for HCC by providing validation in a large, independent multicentre cohort. They conclude that this score could allow evidence-based decisions for clinical management of hepatitis B carriers at variable risk of HCC.

The key question for clinicians is whether or not this risk score can lead to tailored decisions in the management of patients with chronic hepatitis B, such as no surveillance in patients with a low score or a change to more frequent surveillance or use of more sensitive imaging techniques in those with a high score. Prospective studies of surveillance every 3-4 months versus 6 months, or use of CT or MRI rather than ultrasound in high-risk patients with chronic hepatitis B would be needed before a clinician could with confidence change from the standard recommendation of ultrasonography every 6 months, usually with α-fetoprotein.\(^1\) The population that was the basis of the Yang and colleagues’ risk score did not include patients with cirrhosis, which is known to be the major risk factor for HCC and is present in up to three-quarters of HBV-related HCC.\(^5\) Moreover, cirrhosis was the most important independent risk score for development of HCC in Yuen and colleagues’ risk score.\(^4\)

Many Asian–American patients who are undergoing antiviral therapy have undetectable HBV DNA, normal alanine aminotransferase concentrations, and are HBeAg negative; they would have a low risk score but yet fit the criteria for surveillance recommended in the AASLD guidelines on the basis of their age or other factors (eg, presence of cirrhosis or a family history of HCC). How to resolve the different advice provided by a risk score versus a society guideline is a dilemma for the clinician. Risk scores might be most helpful in identification of patients with a very low risk of HCC who do not need surveillance, rather than leading to a change in surveillance practices in patients with a high score. Additionally, the incidence of HCC differs according to the geographical distribution of risk factors, and surveillance strategies derived from a Taiwanese or Asian populations might not apply globally. Finally, scoring systems should include known risk factors such as the presence of cirrhosis, use of alcohol, and family history of HCC, and should be validated in white and African patients who are often infected in adulthood and whose risks for HCC differ substantially from those in Asian patients with chronic HBV infection dating from birth or early childhood. Thus, risk scores for the development of HCC are in the preliminary stages of development and not yet ready for widespread use in practice.

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I have no conflicts of interest.


Authors’ reply
Although our predictive score for risk estimation of hepatocellular carcinoma in patients with chronic hepatitis B was externally validated,\(^1\) we agree with Emmet Keeffe\(^7\) that further validation is needed in patients of other ethnic origins and in those infected with hepatitis B virus later in life. Family history of hepatocellular carcinoma and alcohol consumption are also important factors, but present problems for clinicians in terms of data collection. Subsequent revisions to this risk calculator will depend on the wide