HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

The BALAD-2 and GALAD Biomarker Models for Hepatocellular Carcinoma

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G&H Do biomarkers currently have a role in hepatocellular carcinoma?

PJ The role of biomarkers in hepatocellular carcinoma (HCC) is controversial. For example, the best-known biomarker in HCC is α-fetoprotein (AFP), which has been around for more than 50 years. Many hepatologists use AFP as a diagnostic aid, but there are probably an equal number who do not think that the biomarker is any help because it is relatively nonspecific. Thus, there are 2 schools of thought: one that believes that there is a role for biomarkers in HCC and one that does not.

G&H How and why were the BALAD-2 and GALAD biomarker models developed?

PJ Doctors in Japan, which has a high incidence and prevalence of HCC, have used the biomarkers AFP, des-γ-carboxyprothrombin (DCP), and Lens culinaris agglutinin-reactive AFP (AFP-L3) for many years for the diagnosis of HCC as well as for undertaking surveillance of patients who are at high risk for the disease. Although there is still a need for more sensitive and specific biomarkers for HCC, an alternative approach is to combine existing ones. Thus, markers were combined in the BALAD (bilirubin, albumin, AFP-L3, AFP, and DCP) and GALAD (gender, age, AFP-L3, AFP, and DCP) models in an attempt to improve the prognostication and diagnosis, respectively, of HCC.

The prognostic BALAD model was developed by Dr Hidenori Toyoda and colleagues in 2005. Subsequently, my colleagues and I in Birmingham, United Kingdom, undertook a close collaboration with Toyoda and colleagues to combine their original data with some data of our own and perform a rigorous statistical analysis to develop BALAD-2. This biomarker model is very similar to the original BALAD model; it just involves a more complex statistical analysis and provides a slightly better performance.

The diagnostic GALAD model uses the same 3 biomarkers as the BALAD model but considers gender and age. My colleagues and I in Birmingham used data on AFP, AFP-L3, and DCP to build a rigorously validated statistical diagnostic model. This model was then validated in collaboration with Toyoda and colleagues.

The main difference between individual biomarker use by Toyoda and colleagues and use of the GALAD model is that the former used predefined biomarker cutoff points for being positive or negative, whereas the GALAD model considers the individual biomarkers in their continuous format. Using a continuous format is probably better than using predefined cutoffs; the latter "wastes" much information.

G&H Why did you and your colleagues choose to use AFP, AFP-L3, and DCP when building HCC biomarker models?

PJ Those biomarkers were chosen because they are available on a commercial platform, they are very well-characterized assays, and there is a vast amount of data on them from Japan for further analysis.

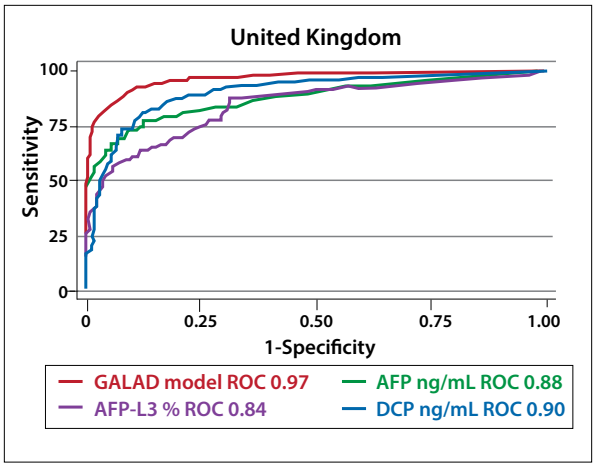

Figure 1. ROC curves for the GALAD score and its individual components. The GALAD score is significantly better than any of the individual components.

AFP, α-fetoprotein; AFP-L3, Lens culinaris agglutinin-reactive AFP; DCP, des-γ-carboxyprothrombin; GALAD, gender, age, AFP-L3, AFP, and DCP; ROC, receiver operating characteristic.

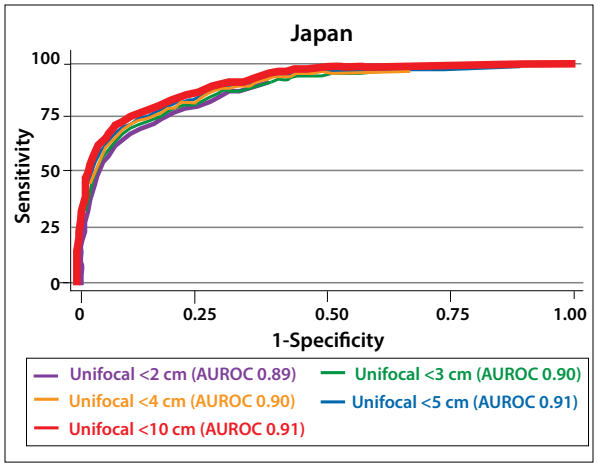

Figure 2. ROC curves for Japanese patients according to tumor size. The curves are almost superimposable irrespective of tumor size.

AUROC, area under the ROC curve; ROC, receiver operating characteristic.

G&H Based upon the data available thus far, how does the performance of the GALAD model compare with that of the individual biomarkers?

PJ The best way of examining the performance of a model such as GALAD is to look at its area under the receiver operating characteristic curve. This number provides a general description of how good a model is. AFP, AFP-L3, and DCP all exhibit some degree of diagnostic discrimination. When these 3 biomarkers are combined, diagnosis improves in all populations and stages of the disease. The GALAD model is clearly better than using the biomarkers separately (Figure 1).

G&H How sensitive and specific is the GALAD model?

PJ It is important to keep in mind that sensitivity and specificity are reciprocally related, so if sensitivity is high, then specificity goes down, and vice versa. Optimal sensitivity and specificity are in the order of 0.85—ie, approximately 85% sensitive and approximately 85% specific. However, the sensitivity and specificity of the GALAD model vary across different subgroups and disease stages, which is why the area under the receiver operating characteristic curve is better to use.

G&H Has the GALAD model been examined in terms of different underlying liver disease and race?

PJ Yes. The model seems to be roughly as effective irrespective of disease etiology. An abstract presented at last year's European Association for the Study of the Liver meeting by Dr Ju Dong Yang, on behalf of colleagues at the Mayo Clinic including lead investigator Dr Lewis Roberts, examined the use of the GALAD model in various subgroups, including different races, in several large US centers. Under the aegis of the National Cancer Institute Early Detection Research Network, the researchers concluded that the performance of the GALAD model for HCC diagnosis in a multicenter US cohort was excellent. They also found that the sensitivity, specificity, and area under the receiver operating characteristic curve varied somewhat according to ethnicity, etiology, and disease stage.

G&H Has the GALAD model been used in early- and late-stage HCC?

PJ Yes, the abstract by Yang and colleagues found that the GALAD model works well in both settings. In a study that my colleagues and I published, the GALAD model worked well irrespective of tumor size, which was a surprise (Figure 2).

G&H Does the GALAD model have any other roles in HCC?

PJ That is an area of active investigation. The GALAD score appears to be proportional to the tumor cell mass. Thus, in the future, the GALAD model might be useful for monitoring treatment. More controversially, the score

appears to be elevated before cancer can be seen on a scan, which means that it may have a role in the surveillance setting for very early diagnosis of HCC. However, more research is needed on both of these issues.

G&H What studies have been conducted using the BALAD-2 model?

PJ A large, recent, international, multicenter study conducted by Dr Sarah Berhane and colleagues (of which I was a part) described the prognostic use of BALAD-2 in detail. We concluded that BALAD-2 provides an extremely good indication of the prognosis of HCC patients irrespective of etiology and cancer size. This was confirmed in a recent nationwide study from Japan conducted by Toyoda and colleagues. BALAD-2 showed clear prognostic power and a modest improvement in prognostic performance over the original BALAD model across all stages of disease and all etiologies.

G&H What are the advantages and disadvantages of the GALAD model?

PJ One advantage is that it is entirely objective; it does not require any subjective factors or interpretation of radiographic images. Another advantage is that it is easy to determine the score, which can be done with an online calculator (eg, at http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/galad) or a smartphone application.

A disadvantage of the GALAD model (which also applies to BALAD-2) is that at present, relatively few laboratories will perform the 3 biomarker assays. Such laboratories are numerous in Japan and are starting to increase in Europe and the United States, but are not yet widespread. A second disadvantage, which is common to all serologic approaches to early diagnosis, is that although the GALAD model may suggest that an HCC has developed, it does not say where it is. Only imaging can accomplish this task.

G&H What are the advantages and disadvantages of the BALAD-2 model?

PJ I think that the BALAD-2 score is very much a secondary output from these 3 biomarkers, with the GALAD score being more important. It is fair to say that a medical center would not measure AFP, AFP-L3, and DCP solely to obtain a BALAD-2 score. The reason that these biomarkers are measured routinely is to obtain a GALAD score (ie, for diagnosis). Because the 3 biomarkers are being measured anyway, the information can be used for the BALAD-2 model for prognosis.

G&H Do you think that these models will eventually replace the use of individual biomarkers and/or imaging?

PJ It remains to be seen. However, there will always be a need for radiologic imaging. As previously mentioned, the GALAD score can indicate whether a patient has a cancer or is likely to develop one. What it cannot do is show where cancer is located in the liver. For many forms of treatment, particularly early treatment, it is necessary to know exactly where the cancer is located. Most likely, if these models prove to be successful in prospective trials, they would be used in combination with current imaging approaches.

G&H Are other biomarker models also being investigated in HCC?

PJ Numerous biomarker models are being examined. However, in many cases, these are developed in individual laboratories and reported, and then no further steps are taken because the assays are not robust enough to be transferred consistently around the world.

G&H What are the next steps in research?

PJ The most important next step is prospective study, and at least 2 such studies are currently being conducted. One is being performed in Toronto, Canada, with Dr Morris Sherman as the lead investigator. The other study is being led by Dr Hashem El-Serag in Texas. Both will be reporting preliminary findings in the next few weeks. These studies will help determine whether the biomarkers individually or as combined in the GALAD model will become more widely applied.

Dr Johnson has no relevant conflicts of interest to disclose.

Suggested Reading

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