Role of the Galad and Balad-2 Serologic Models in Diagnosis of Hepatocellular Carcinoma and Prediction of Survival in Patients

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BACKGROUND & AIMS: **GALAD and BALAD-2 are statistical models for estimating the likelihood of the presence of hepatocellular carcinoma (HCC) in individual patients with chronic liver disease and the survival of patients with HCC, respectively. Both models use objective measures, particularly the serum markers α-fetoprotein (AFP), AFP-L3, and des-γ-carboxyprothrombin. We aimed to validate these models in an international cohort of patients with HCC and assess their clinical performance.**

METHODS: **We collected data on cancer diagnosis and outcomes of 6834 patients (2430 with HCC and 4404 with chronic liver disease) recruited from Germany, Japan, and Hong Kong. We also collected data from 229 patients with other hepatobiliary tract cancers (cholangiocarcinoma or pancreatic adenocarcinoma) and 92 healthy individuals (controls). For reference, the original UK cohort (on which the GALAD model initially was built and BALAD-2 was validated) was included in the analysis. We assessed the effects of tumor size and etiology on GALAD model performance, and its ability to correctly discriminate HCC from other hepatobiliary cancers. We assessed the performance of BALAD-2 in patients with different stages of HCC.**

RESULTS: **In all cohorts, the area under the receiver operating characteristic curve (AUROC), quantifying the ability of GALAD to discriminate patients with HCC from patients with chronic liver disease, was greater than 0.90—similar to the series on which the model originally was built (AUROC, 0.97). GALAD discriminated patients with HCC from those with other hepatobiliary cancers with an AUROC value of 0.95; values were slightly lower for patients with small unifocal HCCs, ranging from 0.85 to 0.95. Etiology and treatment of chronic viral hepatitis had no effect on the performance of this model. BALAD-2 analysis assigned patients with HCC to 4 distinct prognostic groups—overall and when patients were stratified according to disease stage.**

Abbreviations used in this paper: AFP, α-fetoprotein; AIC, Akaike information criterion; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; CLD, chronic liver disease; DCP, des-γ carboxyprothrombin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ROC, receiver operating characteristic; USS, ultrasound scan.

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CONCLUSIONS: **We validated the performance of the GALAD and BALAD-2 models for the diagnosis of HCC and predicting patient survival, respectively (based on levels of the serum markers AFP, AFP-L3, and des-γ-carboxyprothrombin), in an international cohort of almost 7000 patients. These systems might be used in HCC surveillance and determination of patient prognosis.**

Keywords: Liver Cancer; Prognostic Marker; Diagnostic; Quantification.

We recently developed a serum-based tool (GALAD) for the detection of hepatocellular carcinoma (HCC) based on the objective measures of sex, age, and the 3 serologic biomarkers of α-fetoprotein (AFP), AFP-L3, and des-γ-carboxyprothrombin (DCP),[2] all of which are commercially available on a single standard platform.[3] The model has the potential to be used in the surveillance setting and may mitigate some of the limitations of ultrasound scanning (USS), including limited sensitivity in obese patients and in patients with advanced cirrhosis. The former is of particular importance because obesity-related HCC accounts for an increasing percentage of HCC.[4–8] However, the model has not been validated in other countries where the underlying etiology of HCC is different. Although it appeared to perform as well in patients with early disease (defined as tumor size < 5 cm) as it did in patients with advanced disease, we did not undertake detailed analysis of the impact of tumor size on the utility of the model. This is of importance in the screening setting because the earlier the disease is detected the better the chance of curative treatment.

The same 3 biomarkers were combined with liver function tests (serum bilirubin and albumin) by Toyoda et al[9] to form the BALAD model for prognostication in HCC. A more rigorous statistical approach generated a second model (BALAD-2) that applied the same variables in a continuous rather than a categoric manner,[10] but, again, the model has not been validated in the international setting or at different disease stages.

We describe the application of these 2 models to cohorts from Germany, Japan, and Hong Kong.

Patients and Methods

We used cohorts from Germany, Japan, and Hong Kong (Table 1). Both HCC and chronic liver disease (CLD) cohorts were used for GALAD validation and HCC patients were used only for BALAD-2 validation. CLD refers to liver disease that has lasted over a period of 6 months. Table 1 also reports the percentage of cases with cirrhosis.

The German cohort came from 4 large centers based at the University Hospital Essen (collected between 2005 and 2008), Hannover Medical High School (collected between 2008 and 2014), Leipzig (Evangelisches Krankenhaus Duisburg-Nord, collected between 2010 and 2013), and Mainz University Medical Centre (collected between 2003 and 2012). Overall, they comprised 1278 patients (275 HCC and 1003 patients with CLD alone).

The Japanese patients comprised 4476 patients (1514 with HCC and 2962 with CLD alone) and these were recruited from Ogaki Municipal Hospital where they initially were diagnosed as having HCC between 1988 and 2013.

The Hong Kong cohort (247 HCC patients) was recruited from the Prince of Wales Hospital, Department of Clinical Oncology, Chinese University of Hong Kong between 2009 and 2013.[11]

For reference, the original UK cohort (on which the GALAD model initially was built and BALAD-2 was validated) was included in the analysis. These patients were recruited at the Queen Elizabeth Hospital (Birmingham, UK) and the NHS Foundation Trust (Newcastle Upon Tyne) between 2007 and 2012. The Birmingham cohort comprised 670 patients (331 with HCC and 339 with CLD alone), and the Newcastle cohort comprised 163 patients (63 with HCC and 100 with CLD alone).

We also included 229 patients with other hepatobiliary tract cancers (cholangiocarcinoma and pancreatic adenocarcinoma) (Table 2), and 92 healthy controls (Table 1) recruited also from the Queen Elizabeth Hospital (Birmingham, UK) between 2006 and 2012 and 2009 and 2011 respectively, to test the ability of the GALAD model to discriminate HCC from other hepatobiliary cancers and healthy controls. The hepatobiliary cohort was divided further into 3 subgroups: intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and pancreatic adenocarcinoma.

None of the CLD control group had evidence of HCC at the time the relevant serum sample was taken or within a minimum follow-up period of 9 months (Table 1). They were considered typical of those who would be included in a surveillance program. In all cohorts, the HCC patients had the 3 biomarkers measured within ± 1.7 months of HCC diagnosis and before any treatment was administered.

The diagnosis of HCC was made according to international guidelines.[4,5] Patients in the control groups had established chronic liver disease (on the basis of liver biopsy and/or typical clinical and imaging features). All patients had the 3 constituent biomarkers measured using the μTASWako i30 autoanalyzer (Wako Pure Chemical Industries, Ltd, Osaka, Japan). Patients with HCC were classified as having early (those receiving potentially curative therapy), intermediate (intra-arterial therapies), or advanced disease (systemic chemotherapy or supportive care).