Diagnosis Of Hepatocellular Carcinoma Using A GALAD Model By Objective Clinical And Serological Factors

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Background

Late diagnosis of hepatocellular carcinoma (HCC) frequently results in poor patient outcome. Routine surveillance is recommended to detect early stage HCC so as to be able to apply curative treatments. The most common tests used for surveillance are alpha-fetoprotein (AFP) and ultrasound (US). However, interpretation of US can be challenging without comparison to previous imaging results and can be limited in patients who are obese or have severe background liver cirrhosis. US quality is user dependent which may affect its ability to be used to detect HCC lesions early. Therefore, reliable serological biomarkers are needed. *Lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3) and des-gamma-carboxy prothrombin (DCP) are biomarkers widely used for surveillance in Japan. These biomarkers are complementary and their simultaneous measurement is recommended. In this study, we describe the use of a newly developed and validated statistical model ("GALAD") using the three biomarkers and objective factors (age and gender) for HCC diagnosis.

Procedure

Step 1
Model Development

Logistic regression analysis using the data set from Birmingham.

Five factors were identified on univariate analysis that discriminated between HCC and non-HCC.

→ Gender, Age, AFP-L3, AFP, DCP

Step 2
Model Validation

The model was built on a dataset from Birmingham and internally validated on a second dataset from Birmingham then externally validated on a Newcastle dataset.

The coefficients were set for the model.

→ GALAD Model

Step 3
Model Evaluation

Here, the model is internationally evaluated using the dataset from Ogaki Municipal Hospital.

→ ROC analysis, Sensitivity/ Specificity

Model Development

Table 1. Parameter estimates (se) and odds ratios (95% confidential intervals) of variables based on the model [UK dataset]

Variable	β (se)	Odds Ratio (95% CI)	χ2	p-value
Constant	-10.08 (1.08)	-	-	-
Age	0.09 (0.01)	1.10 (1.07-1.13)	44.87	<0.001
Gender	1.67 (0.33)	5.30 (2.79-10.07)	25.89	<0.001
Log (AFP)	2.34 (0.33)	10.34 (5.40-19.79)	49.73	<0.001
AFP-L3	0.04 (0.01)	1.04 (1.01-1.07)	8.66	0.003
Log (DCP)	1.33 (0.17)	3.77 (2.73-5.21)	64.56	<0.001

Z = -10.08 + 1.67 x [G] + 0.09 x [Age] + 0.04 x [L] + 2.34 x log[AFP] + 1.33 x log[D]

[G]: Gender (0=Female, 1=Male) [L]: AFP-L3 (%)

[Age]: Age (year) [AFP]: AFP (ng/mL)

[D]: DCP (ng/mL)

Model Validation

Table 2. The GALAD model performance [UK dataset]

	TRUE HCC (n)	TRUE non-HCC (n)	FALSE HCC (n)	FALSE non-HCC (n)	Sensitivity	Specificity	Cut-off
Max. Sens. (Spec.=0.80)	367	347	87	15	96%	80%	-1.36
Max. Spec. (Sens.=0.80)	306	420	14	76	80%	97%	0.88
Max. Sens.+Spec.	356	385	49	26	93%	89%	-0.63

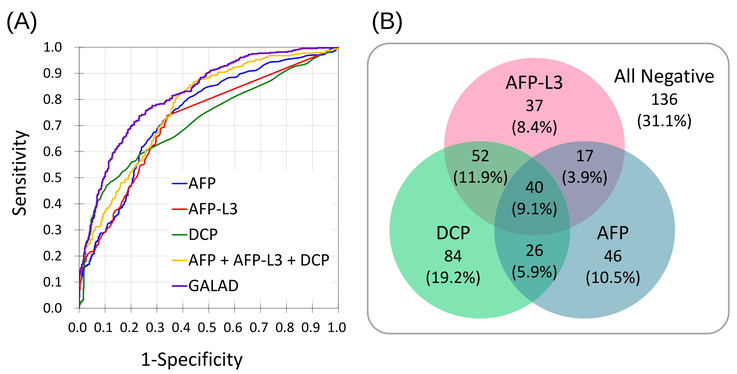
Patient Characteristics

Table 3. Characteristics of HCC and chronic liver disease (CLD) patients

Variable	Ogaki, Japan		Birmingham, UK		Newcastle, UK	
	HCC (n=438)	CLD (n=607)	HCC (n=331)	CLD (n=339)	HCC (n=63)	CLD (n=100)
Demographics						
Median age (25%-75% quartile)	69 (62-75)	66 (57-73)	66 (59 -73)	53 (45-63)	69 (6275)	64 (57-69)
Gender (Male: Female)	317:121	298:309	272:59	214:125	53:10	42:58
Etiology						
HCV:HBV:B+C:Other	328:56:9:45	378:105:10 :114	43:30:2:159 (Alcohol: 81)	74:58:6:128 (Alcohol: 53)	0:0:0:54 (Alcohol: 27)	0:0:0:100 (Alcohol: 17)
HCC Biomarkers, Median (25%-75% quartile)						
AFP (ng/mL)	9.3 (5.1-29.4)	3.3 (2.0-7.1)	57.0 (8.3-1438.0)	2.8 (2.0–4.7)	44.5 (6.1 – 1501.9)	3.2 (2.3 – 4.7)
AFP-L3 (%)	5.0 (0.5-8.4)	0.5 (0.5-4.6)	16.6 (7.0-51.9)	0.5 (0.5–7.1)	24.5 (8.1 – 49.4)	0.5 (0.5–7.7)
DCP (ng/mL)	0.40 (0.22-2.52)	0.22 (0.16-0.3)	20.8 (2.6-169.7)	0.35 (0.27 – 0.60)	16.3 (3.0–102.7)	0.5 (0.4–0.8)
Liver Function Tests, Median (25%-75% quartile)						
Albumin (g/dL)	3.7 (3.4-4.0)	4.0 (3.6-4.2)	3.9 (3.4-4.3)	4.4 (4.0-4.6)	3.6 (±0.56)	4.4 (4.1-4.7)
Bilirubin (mg/dL)	0.8 (0.6-1.1)	0.8 (0.6-1.0)	1.0 (0.6-1.6)	0.6 (0.5-1.1)	1.0 (0.7-1.8)	0.5 (0.4-0.8)
Child-Pugh						
A:B:C	347:83:8	507:89:11	245:73:10	291:43: 4	40:12:11	NK

Results

Figure 1. (A) Receiver operating characteristic curves and (B) distribution of patients with various patterns of positivity for the biomarkers (Cut-off: AFP, 20 ng/mL; AFP-L3, 7%; DCP, 0.48 ng/mL) [Ogaki dataset]



Results

Table 4. Sensitivity, Specificity, and Area under the curve (AUC) for the biomarkers and the GALAD model [Ogaki dataset]

	Cut-off*	Sensitivity	Specificity	AUC	*P* value
Individual					
AFP	20 ng/mL	29.5%	89.8%	0.740	
AFP-L3	7%	33.3%	87.0%	0.716	
DCP	0.48 ng/mL	46.1%	89.8%	0.717	
Combination					
AFP + AFP-L3 + DCP	Same as above	68.9%	73.1%	0.768	<.0001**
GALAD Model	-1.41	73.7%	76.8%	0.821	

* Cut-off points for three biomarkers were based on the guideline of the Japan Society of Hepatology and our previous studies. For the GALAD model, the optimum cut-off point was set from the ROC analysis.

** The *P* value was comparison of AUC between 3 biomarkers and the GALAD model.

Table 5. Area under the curve (AUC) for the GALAD model by maximum tumor size (cm)

Maximum	Ogaki		UK	
tumor size (X)	n	AUC	n	AUC
X ≤ 2 cm	200	0.782	35	0.893
2 < X ≤ 3 cm	111	0.829	59	0.940
3 < X ≤ 5 cm	81	0.862	94	0.958
5 cm < X	46	0.895	164	0.980
All	438	0.821	352	0.959

Discussion

- The GALAD model developed for the discrimination between HCC and non-HCC gave higher sensitivity and specificity compared to the conventional combined use of AFP, AFP-L3, and DCP.
- The model gave consistently high figures for the AUC in the datasets from both Ogaki and UK (0.821 and 0.959, respectively).
- The AUC values of the subgroup of patients who had a tumor sizes over 2 cm were higher than that of patients with tumors less than 2 cm (0.782 and 0.893 for Ogaki and UK, respectively).
- The model may help diagnosis of HCC on the grounds of objective clinical and serological factors.

References

- Johnson P, *et al*. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev. 2013 *in press*

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