THE 'GALAD SCORE' FOR THE SEROLOGICAL DETECTION OF HEPATOCELLULAR CARCINOMA: INTERNATIONAL VALIDATION AND ASSESSMENT OF THE INFLUENCE OF TUMOUR SIZE AND AETIOLOGY ON MODEL UTILITY

Sarah Berhane[1], Hidenori Toyoda[2], Toshifumi Tada[2], Takashi Kumada[2], Chiaki Kagebayashi[3], Shinji Satomura[3], Nora Schweitzer[4], Arndt Vogel[4], Michael P Manns[4], Julia Benckert[5], Thomas Berg[5], Jan Best[6], Alexander Dechêne[6], Guido Gerken[6], Joerg F Schlaak[7], Helen Reeves[8,9], Philip Johnson[1,10]

[1]University of Liverpool, Liverpool, UK; [2]Ogaki Municipal Hospital, Gifu, Japan; [3]Wako Life Sciences, Inc., Mountain View, CA, U.S.A; [4]Hannover Medical High School, Hannover, Germany; [5]University Hospital Leipzig, Leipzig, Germany; [6]University Hospital Essen, University Duisburg-Essen, Essen, Germany; [7]Evangelisches Krankenhaus Duisburg-Nord, Duisburg, Germany; [8]Northern Institute for Cancer Research, Newcastle upon Tyne, UK; [9]Newcastle upon Tyne NHS Foundation Trust, The Freeman Hospital, Newcastle upon Tyne, UK; [10]The Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK

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BACKGROUND

A statistical model, developed in the UK, permits estimation of the likelihood that hepatocellular carcinoma (HCC) is present in individual patients with chronic liver disease (CLD) using objective measures, particularly the serological tumor markers (AFP, AFP-L3 and DCP).

This model (1), which has the potential to be used in the screening/surveillance setting, has not been validated in an international setting.

OBJECTIVES

To validate the model in an international setting by application to cohorts from Japan and Germany.

To compare the model with one where the biomarkers are used individually or to the conventional approach of using these biomarkers in the Japanese screening program.

Assess the influence of aetiology and tumour size on model utility.

MATERIALS & METHODS

Cohorts comprising 4476 patients from Ogaki, Japan (1514 HCCs and 2962 CLDs) and 1086 from three centres in Germany, namely Hannover, Leipzig and Essen (238 HCCs and 848 CLDs) were recruited.

We also included, for reference, the original UK cohort on which the model was developed (394 HCCs and 439 CLDs) (1). We assessed the change in sensitivity, specificity and area under the ROC curve (AUROC).

In each case sera and related clinical features were collected by investigators independent of the laboratory (Wako Life Sciences, Inc.) in which the biomarker assays were performed and the group performing the statistical analysis.

RESULTS

Table 1: Demographics of the cohorts involved in validation of the model.

Table 1. Characteristics of HCC and CLD patients

	UK (Birmingham and Newcastle)		Japan		Germany (Hanover, Leipzig and Essen)	
Variable	**HCC (n=394)**	**CLD (n=439)**	**HCC (n=1514)**	**CLD (n=2962)**	**HCC (n=238)**	**CLD (n=848)**
Demographics						
Median Age	66.9 (59.6 – 73.5)	56.1 (46 – 64)	69 (62 – 75)	63 (53 – 71)	66 (59 – 71)	49 (39 – 59)
Mean Age (±SD)	65.8 (±9.7)	54.9 (±13.7)	67.8 (±9.4)	61.0 (±13.7)	64.9 (±9.2)	48.8 (±14.3)
Gender (% Male)	82.5	58.3	71.3	48.0	82.8	54.0
Aetiology						
HCV : HBV : Other (%)	18.3 : 9.0 : 72.7 n=377	24.1 : 14.3 : 61.7 n=428	69.2 : 15.4 : 15.4 n=1495	45.4 : 24.1 : 30.5 n=2920	22.7 : 11.6 : 65.8 n=225	28.1 : 33.3 : 38.6 n=832
HCC Biomarkers						
AFP, ng/ml	53.1 (7.6 – 1460.9) n=394	2.9 (2.1 – 4.7) n=438	22.3 (7.0 – 171.6) n=1514	2.5 (1.8 – 3.9) n=2962	44.4 (7.7 – 793.4) n=238	3 (1.8 – 5.5) n=848
L3, %	17 (7.2 – 51.8) n=382	1 (1 – 7.2) n=438	4.9 (0.5 – 16.8) n=1514	0.5 (0.5 – 0.5) n=2962	14.6 (5.9 – 47) n=238	0.1 (0.1 – 6) n=848
DCP, ng/ml	20.1 (2.6 – 169.6) n=383	0.4 (0.3 – 0.7) n=438	0.7 (0.2 – 9.5) n=1514	0.20 (0.1 – 0.2) n=2962	11.5 (1.5 – 153.0) n=238	0.4 (0.2 – 0.6) n=848
Tumor Characteristics						
% Solitary	46.7 n=315	N/A	55.0 n=1512	N/A	35.5 n=228	NA
Maximum tumor size (cm), %						
< 5cm : ≥ 5cm	48.1 : 51.9 n=337	N/A	76.6 : 23.4 n=1490	N/A	45.5 : 54.5 n=202	NA

Abbreviations: AFP, alpha-fetoprotein; CLD, chronic liver disease; DCP, Des-gamma carboxyprothrombin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalised ratio; N/A, not applicable; NA, not available; SD, standard deviation. All continuous variables are presented as median (with interquartile range).

GALAD score:

Z=-10.08 + 0.09 x age + 1.67 x sex + 2.34 log (AFP) + 0.04 x AFP-L3 + 1.33 x log (DCP)

where Probability of HCC= exp(Z)/(1+exp(Z))

Figure 1: Applying the model on the validation cohorts from Japan and Germany yielded similar AUROC figures to that of the original cohort (UK), confirming model utility.

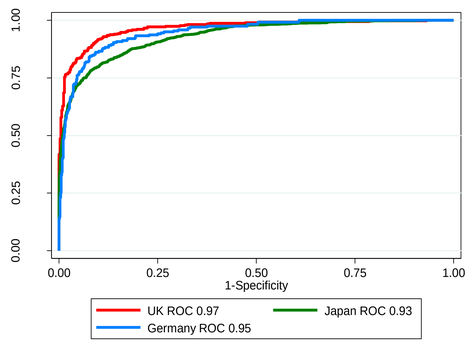

Figure and Table 2: In all three cohorts, the figures for the optimised sensitivity and specificity (Table 2), and the AUROC derived from the model (Figures 2a, 2b and 2c) were superior to those obtained if the biomarkers were used individually or combined (as currently used in clinical practice in Japan).

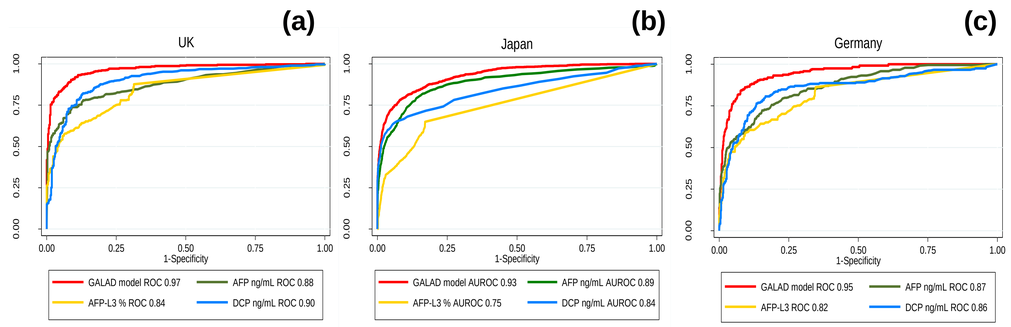

Table 2: GALAD model performance

Country	Biomarker/model	Cut-off*	AUC	Sensitivity %	Specificity %	Correctly Classified %
UK	GALAD model	-0.63	0.97	91.6	89.7	90.6
	AFP	20 ng/mL	0.88	60.7	96.4	79.5
	AFP-L3	7%	0.84	75.4	73.5	74.4
	DCP	0.48 ng/mL	0.90	62.4	93.8	79.2
	AFP + AFP-L3 +DCP**	Same as above	0.75	99.2	50.0	72.9
Japan	GALAD model	-1.44	0.93	81.4	89.1	86.5
	AFP	20 ng/mL	0.89	51.3	97.3	81.8
	AFP-L3	7%	0.75	41.2	91.8	74.7
	DCP	0.48 ng/mL	0.84	57.3	97.4	83.8
	AFP + AFP-L3 +DCP**	Same as above	0.84	79.3	88.3	85.3
Germany	GALAD model	-0.45	0.95	86.1	90.8	89.7
	AFP	20 ng/mL	0.87	57.6	93.2	85.4
	AFP-L3	7%	0.82	70.2	79.0	77.1
	DCP	0.48 ng/mL	0.86	88.2	67.1	71.7
	AFP + AFP-L3 +DCP**	Same as above	0.75	94.5	56.1	64.6

* Cut-off points for three biomarkers were based on the guideline of the Japan Society of Hepatology. For the GALAD model, the optimum cut-off point was set from the ROC analysis.
**The combination (AFP+AFP-L3+DCP) represents the current method of using the markers in Japan. A positive result is recorded if any of the markers exceed their specified cut off point.

Figure and Table 3: Within each cohort, the utility of the model was only slightly lower in the smaller tumors (Figure 3a, 3b and 3c). This is demonstrated by the fall in AUROC value if tumor size was categorized from ≥5cm to <5cm. There was also no significant change in model performance between HBV, HCV and other subgroups, in all three cohorts. The model performed well in all three aetiologies (Figure 3d, 3e and 3f). Sensitivity and specificity data are shown in Table 3.

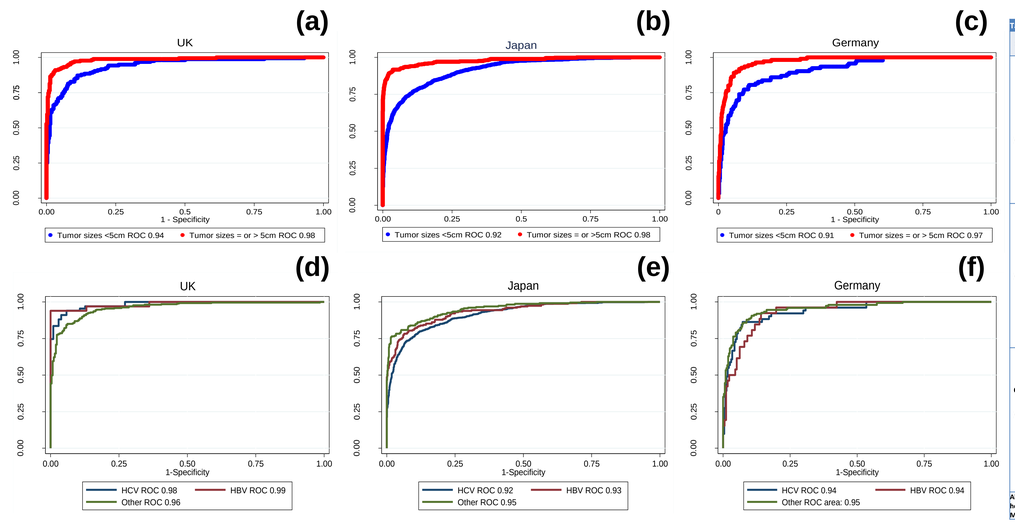

Table 2. GALAD model performance

Country	Set	AUC	Sensitivity %	Specificity %	Correctly Classified %
UK (cut-off= -0.63)	Whole cohort (382 HCC, 437 CLD)	0.97 (C.I. 0.96 – 0.98)	91.6	89.7	90.6
	Tumor sizes <5cm (156 HCC, 437 CLD)	0.94 (C.I. 0.92 – 0.96)	84.0	89.7	88.2
	Tumor sizes ≥5cm (178 HCC, 437 CLD)	0.98 (C.I. 0.97 – 0.99)	97.2	89.7	91.9
	HCV positive cohort (67 HCC, 103 CLD)	0.98 (C.I. 0.97 – 1.0)	91.0	94.2	92.9
	HBV positive cohort (33 HCC, 61 CLD)	0.99 (C.I. 0.96 – 1.00)	87.9	100.0	95.7
	Other aetiology (267 HCC, 262 CLD)	0.96 (C.I. 0.95 – 0.98)	92.5	85.5	89.0
Japan (cut-off= -1.44)	Whole cohort (1514 HCC, 2962 CLD)	0.93 (C.I. 0.92 – 0.94)	81.4	89.1	86.5
	Tumor sizes <5cm (1142 HCC, 2962 CLD)	0.92 (C.I. 0.91 – 0.93)	77.3	89.1	85.8
	Tumor sizes ≥5cm (370 HCC, 2962 CLD)	0.98 (C.I. 0.97 – 0.99)	94.1	89.0	89.6
	HCV positive cohort (1035 HCC, 1325 CLD)	0.92 (C.I. 0.91 – 0.93)	82.6	84.2	83.5
	HBV positive cohort (230 HCC, 704 CLD)	0.93 (C.I. 0.92 – 0.95)	73.9	95.5	90.2
	Other aetiology (230 HCC, 891 CLD)	0.95 (C.I. 0.94 – 0.97)	83.9	91.1	89.7
Germany (cut-off= -0.45)	Whole cohort (238 HCC, 748 CLD)	0.95 (C.I. 0.93 – 0.96)	86.1	90.8	89.7
	Tumor sizes <5cm (92 HCC, 748 CLD)	0.91 (C.I. 0.88 – 0.94)	77.2	90.8	89.3
	Tumor sizes ≥5cm (110 HCC, 748 CLD)	0.97 (C.I. 0.96 – 0.98)	92.7	90.6	90.9
	HCV positive cohort (51HCC, 234 CLD)	0.94 (C.I. 0.90 – 0.97)	86.3	90.6	89.8
	HBV positive cohort (26 HCC, 177 CLD)	0.94 (C.I. 0.89 – 0.98)	61.5	93.8	89.7
	Other aetiology (148 HCC, 321 CLD)	0.95 (C.I. 0.93 – 0.97)	89.9	89.4	89.6

Abbreviations: AUC, area under curve; C.I., 95% confidence interval; CLD, chronic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalised ratio; Max. Sens, maximum sensitivity; Max. Spec., maximum specificity ; na, not available.

SUMMARY

GALAD model performance on the validation cohorts was very similar to that obtained in the original UK dataset.

Model utility was better than using the biomarkers individually.

Model utility was slightly reduced in smaller tumours, but unaffected in the different aetiologies.

CONCLUSIONS

The GALAD model for serological diagnosis of HCC has been validated by application to patient cohorts from Germany and Japan.

Having validated the model, its potential role in a clinical surveillance setting will need to be assessed .

REFERENCES

1. Johnson PJ, Pirrie SJ, Cox TF, et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiology Biomarkers & Prevention. 2014;23:144-53.

Contact Information

Sarah Berhane, Department of Molecular and Clinical Cancer Medicine, The Duncan Building, University of Liverpool, Liverpool, L69 3GA, UK. Email: sarah.berhane@liverpool.ac.uk