

Limited use of established risk scores for the prediction of hepatocellular carcinoma in patients with chronic hepatitis D virus infection

R. Iker*^{1,2}, A. Wranke*^{1,2}, H. Schneider¹, H. Wedemeyer^{1,2,3,4}, H. Kefalakes*^{1,2,3,4}, L. Sandmann*^{1,3,4}

¹ Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology, Hannover Medical School, Hannover, Germany

² German Center for Infection Research (DZIF), Hannover-Braunschweig, Germany

³ D-SOLVE: EU-funded Network on individualized management of hepatitis D, Hannover, Germany

⁴ RESIST Cluster of Excellence, Hannover Medical School, Hannover, Germany

Introduction and Aims

- Hepatocellular carcinoma (HCC) is a major health burden and one of the leading causes of cancer-related deaths worldwide.
- Patients with chronic HDV infection (CHD) are at risk of developing HCC.
- In chronic HBV or HCV infection, risk scores are commonly used to predict HCC, but none has been validated in CHD.
- Here, we aim to validate existing HCC risk scores for their predictive potential in patients with CHD.
- In addition, we search for other predictor variables with the ability to improve HCC prediction.

Methods

- Patients with HCC development (CHD-HCC) during FU were identified and matched to patients without HCC development (CHD-non-HCC) based on sex, age, thrombocytes, INR, and bilirubin at a 1:2 ratio. Minimum follow-up of 6 months was required.
- Time points for data collection: first visit to the clinic (BL), 12 (HCC-12) and 6 months (HCC-6) prior to HCC development, and HCC diagnosis (HCC). Comparable time points were selected for the matched CHD-non-HCC cohort with the last one defined as the last available visit.
- Validated HCC risk scores were calculated and compared between the cohorts.
- Search for predictor variables in our cohort was performed using Cox-Regression and binary logistic regression models.

Results

	HCC	Control	p
n	36	72	
Follow up time, years	3.42 [1.48, 6.86]	5.35 [3.27, 7.98]	0.052
Age at first visit, years	46.70 [42.59, 53.31]	47.53 [40.51, 51.66]	0.379
Age at last visit or HCC, years	52.53 [47.78, 59.95]	52.71 [45.10, 60.09]	0.943
Male, N	27 (75.0)	53 (73.6)	1.000
BMI (kg/m ²)	26.46 (3.77)	25.73 (3.61)	0.373
Sodium (mmol/L)	139.50 [137.00, 142.00]	141.00 [139.00, 143.00]	0.059
Creatinin (μmol/L)	66.50 [58.75, 76.00]	68.50 [59.00, 76.75]	0.533
AST (U/L)	69.00 [47.50, 93.50]	71.00 [45.00, 119.50]	0.896
ALT (U/L)	58.00 [41.50, 115.50]	85.00 [44.00, 135.00]	0.237
Gamma-GT (U/L)	64.00 [44.00, 126.25]	65.50 [34.75, 140.25]	0.920
Alkaline phosphatase (U/L)	123.00 [86.00, 157.00]	107.00 [83.00, 140.75]	0.429
Cholinesterase (kU/L)	4.47 [3.30, 5.61]	5.32 [3.91, 6.75]	0.049
Bilirubin (μmol/L)	14.00 [10.00, 28.50]	13.50 [10.00, 20.00]	0.313
Albumin (g/L)	34.50 [29.25, 39.25]	38.00 [35.00, 42.00]	0.003
AFP (μg/L)	9.50 [5.75, 35.42]	5.45 [3.02, 9.15]	0.002
Platelets (x1000/μl)	88000 [58000, 132250]	89000 [57000, 115500]	0.737
INR	1.25 [1.13, 1.38]	1.18 [1.10, 1.28]	0.071
Hemoglobin (g/dL)	13.50 [11.80, 15.03]	14.10 [12.55, 15.17]	0.168
Leukocytes (x1000/μL)	4.35 [3.68, 5.90]	4.20 [3.30, 5.68]	0.267
MELD	6.00 [6.00, 9.93]	6.00 [6.00, 7.40]	0.234
Liver comorbidities			0.393
none	29 (80.6)	63 (87.5)	
MASLD	4 (11.1)	6 (8.3)	
METALD	1 (2.8)	0 (0.0)	
ALD	2 (5.6)	3 (4.2)	
Smoker	17 (47.2)	24 (33.3)	0.208
HCV coinfection	6 (16.7)	10 (13.9)	0.776
HIV coinfection	0 (0.0)	1 (1.4)	1.000
Cirrhosis at first visit	32 (88.9)	53 (73.6)	0.083
Previous decompensation	15 (41.7)	14 (20.6)	0.037
Previous IFN treatment	9 (26.5)	14 (19.4)	0.454
Cirrhosis at last visit or HCC	35 (97.2)	58 (80.6)	0.019
Decompensation(s) along follow up	23 (63.9)	31 (43.1)	0.066

Table 1.

Patient characteristics at first visit (Baseline)

Continuous variables are depicted as median [IQR] or mean (SD), categorical variables as number (frequencies in %). Student's t-test or Mann-Whitney U-test were used to compare continuous variables, Fisher's exact test was used to compare categorical variables.

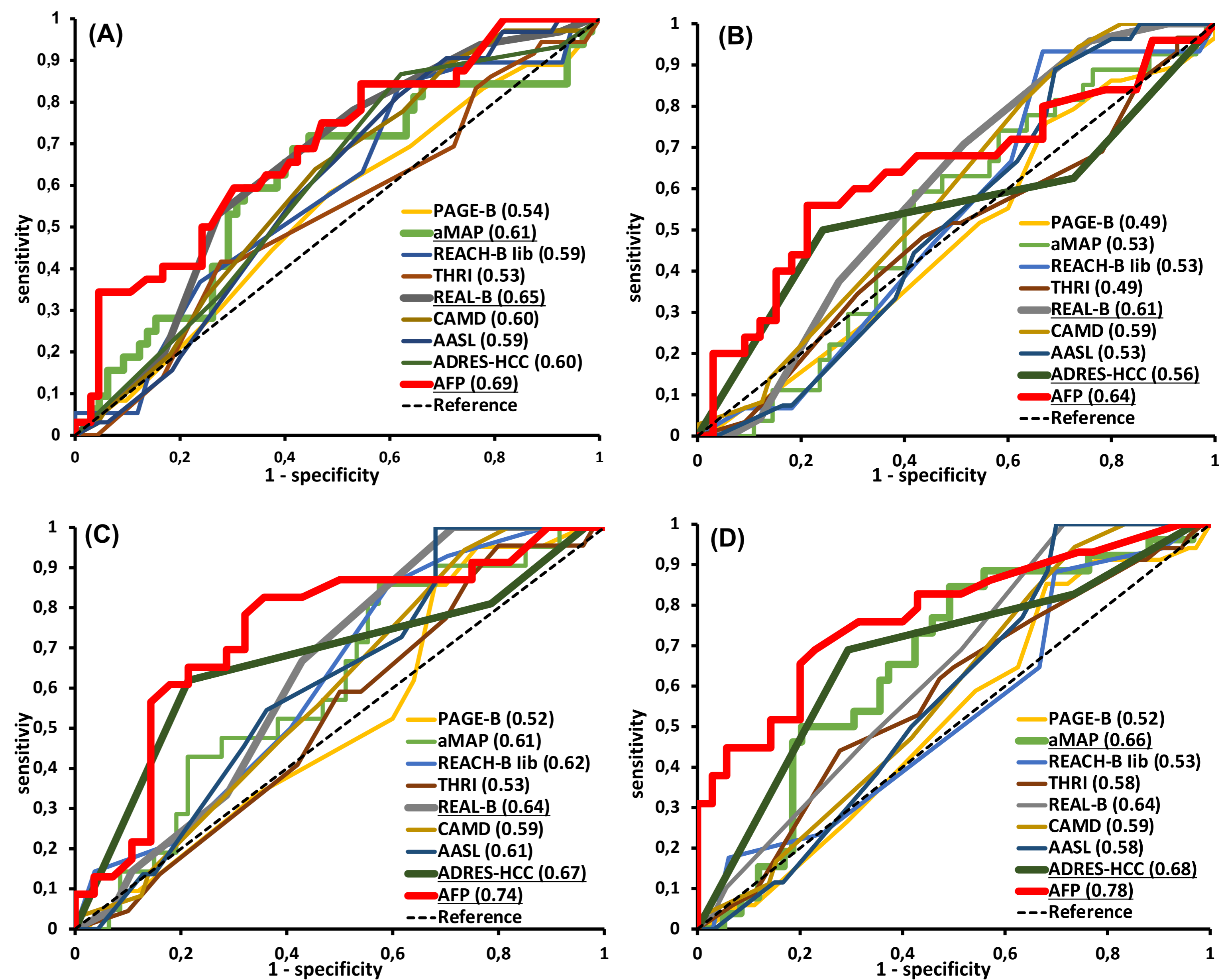


Figure 1.

ROC curves of analyzed risk scores from first visit (A), 12 months prior (B) and 6 months prior (C) to HCC diagnosis or last available follow up (D). The three best scores at every time point are displayed in bold and underlined.

	Parameter	Univariate comparison		Multivariate binary logistic regression	
		Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
First visit at MHH (Baseline)	Sodium	0.85 (0.76 – 0.95)	0.004	0.899 (0.792 – 1.019)	0.096
	Cholinesterase	0.727 (0.598 – 0.884)	<0.001	0.993 (0.742 – 1.331)	0.965
	Albumin	0.851 (0.798 – 0.908)	<0.001	0.858 (0.797 – 0.923)	<0.001
	AFP	1.008 (1.003 – 1.013)	0.002	1.006 (1 – 1.013)	0.062
	Hemoglobin	0.82 (0.695 – 0.968)	0.019	1.055 (0.854 – 1.302)	0.622

Table 2.

Hazard ratios of significant variables for HCC development in univariate and multivariate backward exclusion Cox-Regression. Hazard ratios for every unit increase.

	Parameter	Univariate comparison		Multivariate binary logistic regression		
		Control Group	HCC Group	p value	OR (95% CI)	p value
12 months	Albumin	36.00 [29.00, 43.00]	30.00 [25.00, 38.50]	0.027	0.964 (0.899 – 1.034)	0.311
	AFP	4.50 [3.00, 7.10]	11.00 [3.10, 31.00]	0.063	1.008 (0.996 – 1.021)	0.187
6 months	Albumin	34.00 [28.00, 42.00]	27.50 [24.25, 32.75]	0.010	0.956 (0.885 – 1.034)	0.262
	AFP	3.85 [2.75, 8.00]	11.20 [5.70, 13.65]	0.003	1.02 (0.99 – 1.052)	0.195
Last visit or HCC diagnosis	Albumin	38.00 [30.00, 44.25]	27.00 [23.25, 33.00]	<0.001	0.891 (0.803 – 0.989)	0.03
	AFP	4.30 [2.75, 8.00]	12.90 [8.00, 273.00]	<0.001	1.01 (0.996 – 1.023)	0.158

Table 3.

AFP and Albumin at 12 months, 6 months and HCC or end of follow up respectively depicted with median [IQR]. Univariate comparison using Mann-Whitney-U-Test and multivariate binary logistic regression with Odds Ratios (OR) for every unit increase.

Conclusion

In our cohort, none of the analyzed scores predicted HCC development with sufficient accuracy and consistency. However, HCC risk stratification is essential for the management of CHD patients. Thus, the development of a valid HCC risk score should be addressed in future studies. Close attention should be paid to AFP and albumin, when developing a new prediction system.