Development of Risk Prediction Model for Hepatocellular Carcinoma Progression of Indeterminate Nodules in Hepatitis B Virus-Related Cirrhotic Liver

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BACKGROUND & OBJECTIVES

- During HCC imaging surveillance, cirrhosis-associated nodules with uncertain malignant potential are often detected
- For indeterminate nodules should be differentially diagnosed with RN, DN, early HCC, and "non-nodule–nodule-like lesions"
- Reliable and easy-to-use clinical model for predicting long-term outcome of the indeterminate nodules would be helpful in clinical practice.
- This study was performed to evaluate long-term outcome of indeterminate nodules detected on cirrhotic liver and to develop risk prediction model for HCC progression of indeterminate nodules on HBV-related cirrhotic liver.

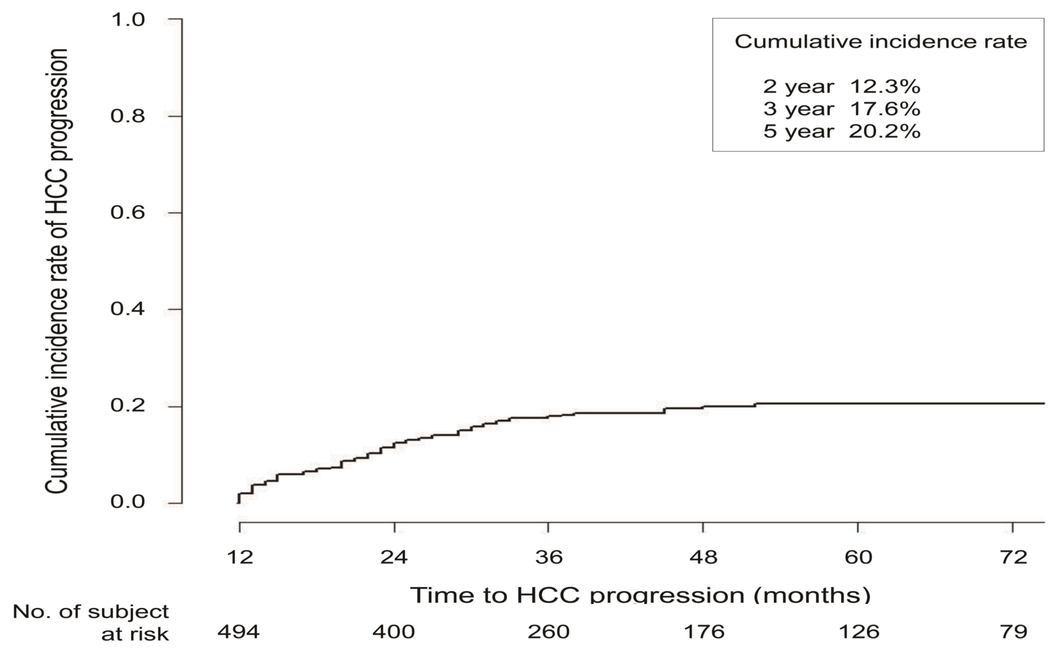
PATIENTS & METHODS

- Retrospective cohort study, Jan 2005 ~ Dec 2013
- Indeterminate nodule : nodular lesions up to 2 cm detected by HCC surveillance CT on cirrhotic liver followed up more than 1 year
- Nodules with definite radiologic features of HCC, such as typical early arterial enhancement and delayed phase wash were excluded, and nodules showing definite benign features, such as typical enhancement pattern of hemangioma or definite cystic lesion, were also excluded.

RESULTS

Table 1. Baseline characteristics of study subjects with and without HCC (*N* = 494)

Variables	subjects without HCC	subjects with HCC	*P*
All included nodular lesions, *N* (%)	***N* = 410 (83.0)**	***N* = 84 (17.0)**	
Size (mm), mean ± SD	10.32 ± 2.52	12.83 ± 3.36	<0.001
Pattern of arterial enhancement			
No arterial enhancement, n (%)	244 (59.5)	47 (56.0)	
Arterial enhancement, n (%)	60 (14.6)	31 (36.9)	<0.001
R/O arterio-portal shunt, n (%)	106 (25.9)	6 (7.1)	
Age (years), mean ± SD [range]	51.58±11.021[19–84]	58.67±10.14[36–82]	<0.001
Male, n (%)	299 (72.9)	66 (73.8)	0.868
Cause of background liver cirrhosis			
Hepatitis B, n (%)	311 (75.9)	62 (73.8)	
Hepatitis C, n (%)	11 (2.7)	8 (9.5)	0.042
Alcoholic, n (%)	67 (16.3)	10 (11.9)	
Other cause, n (%)	21 (5.1)	4 (4.7)	
History of prior HCC, n (%)	16 (3.9)	11 (13.1)	0.002
Platelet (x10^9/L), mean ± SD	131.92 ± 59.62	105.25 ± 51.07	0.001
Albumin (g/dL), mean ± SD	4.13 ± 0.54	3.82 ± 0.58	<0.001
Bilirubin (μmol/L), mean ± SD	1.26 ± 1.13	1.27 ± 0.79	0.432
AFP (ng/mL), mean ± SD	18.60 ± 181.77	115.26 ± 738.61	0.245
ALT (U/L), mean ± SD	52.93 ± 117.96	69.84 ± 112.86	0.277
INR, mean ± SD	1.18 ± 0.26	1.21 ± 0.19	0.599
HBV-associated nodule, *N* (%)	***N* = 311**	***N* = 62**	
HBeAg positivity, n (%)	114 (36.7)	3 (4.8)	0.287
HBV DNA (Log $_{10}$ IU/mL) [mean ± SD]	2.91 ± 2.70	4.38 ± 2.62	<0.001
Patients with antiviral treatment, n (%)	207 (66.6)	33 (53.2)	
Patients without antiviral treatement, n (%)			<0.001
High baseline HBV DNA, n (%)	35 (11.3)	21 (33.9)	
Low baseline HBV DNA, n (%)	69 (22.1)	8 (12.9)	



- Fig 1. Cumulative incidence of HCC progression of indeterminate nodules

Table 2. Risk factors associated with HCC progression (*N* = 494)

Variables	Univariate		Multivariate	
	HR(95% CI)	*P*	HR(95% CI)	*P*
Gender, male	1.05 (0.65-1.71)	0.847		
Age, year	1.06 (1.04-1.08)	<0.001	1.04 (1.01-1.07)	0.002
Background liver disease, CHC	2.99 (144-6.20)	0.003		
Arterial enhancement, Yes	3.42 (2.19-5.34)	<0.001	2.72 (1.58-4.68)	<0.001
Nodule size, > 1cm	9.70 (5.96-15.80)	<0.001	7.18 (4.08-12.67)	<0.001
Child-Pugh class, B and C	2.22 (1.30-3.78)	0.003		
Platelet, <100 x 10^9/L	2.01 (1.23-3.30)	0.006		
Albumin, ≤3.5 g/dL	3.31 (2.00-5.47)	<0.001	1.72 (0.98-3.02)	0.060
Bilirubin, > 2mg/dL	1.13 (0.49-2.62)	0.773		
ALT, > 80 IU/L	2.25 (1.21-4.21)	0.011		
AFP, ≥ 100 ng/mL	7.21 (3.60-14.46)	<0.001	4.48 (1.79-11.19)	0.001
Prior HCC history, yes	3.04 (1.61-5.74)	0.001	3.25 (1.44-7.30)	0.004

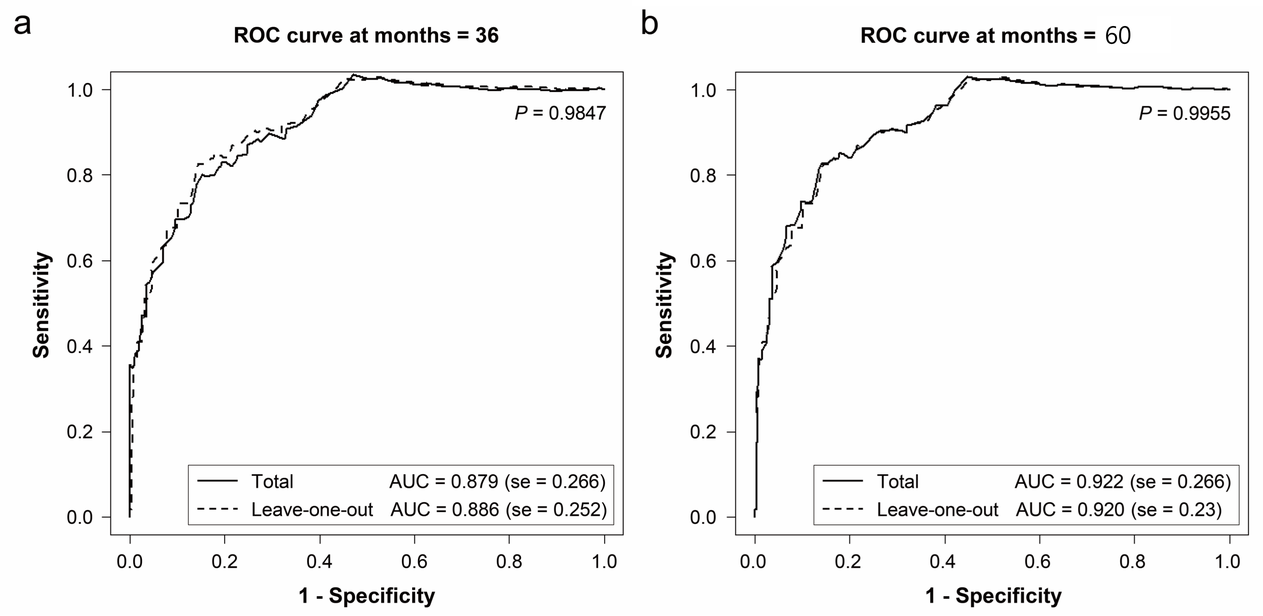
Table 3. Risk factors associated with HCC progression in CHB (*N* = 373)

Variables	Univariate		Multivariate	
	HR(95% CI)	*P*	HR(95% CI)	*P*
Gender, male	0.90 (0.521-1.54)	0.700		
Age, years	1.06 (1.04-1.09)	<0.001	1.05 (1.02-1.08)	0.0033
Arterial enhancement, Yes	3.19 (1.89-5.37)	<0.001	2.45 (1.24-4.84)	0.001
Nodule size, > 1cm	11.92 (6.57-21.65)	<0.001	7.44 (3.75-14.78)	<0.001
Child-Pugh class, B and C	2.50 (1.63-3.85)	<0.001		
Platelet, <100 x 10^9/L	1.88 (1.085-3.27)	0.026		
Albumin, ≤3.5 g/dL	4.81 (2.73-8.48)	<0.001	2.14 (1.10-4.14)	0.024
Bilirubin, > 2mg/dL	1.23 (0.44-3.04)	0.690		
ALT, > 80 IU/L	2.11 (1.06-4.21)	0.034		
AFP, ≥ 100 ng/mL	6.46 (2.93-14.25)	<0.001	4.43 (1.38-14.17)	0.012
Prior HCC history, yes	3.13 (1.55-6.35)	0.002	4.57 (1.93-10.81)	0.006
HBeAg positivity, positive	2.41 (1.47-3.97)	0.001	2.30 (1.27-4.16)	0.006
HBV DNA, High DNA load	2.69 (1.52-4.76)	0.001		
Antiviral treatment, no treatement in high HBV DNA titer	3.18 (1.88-5.39)	<0.001		

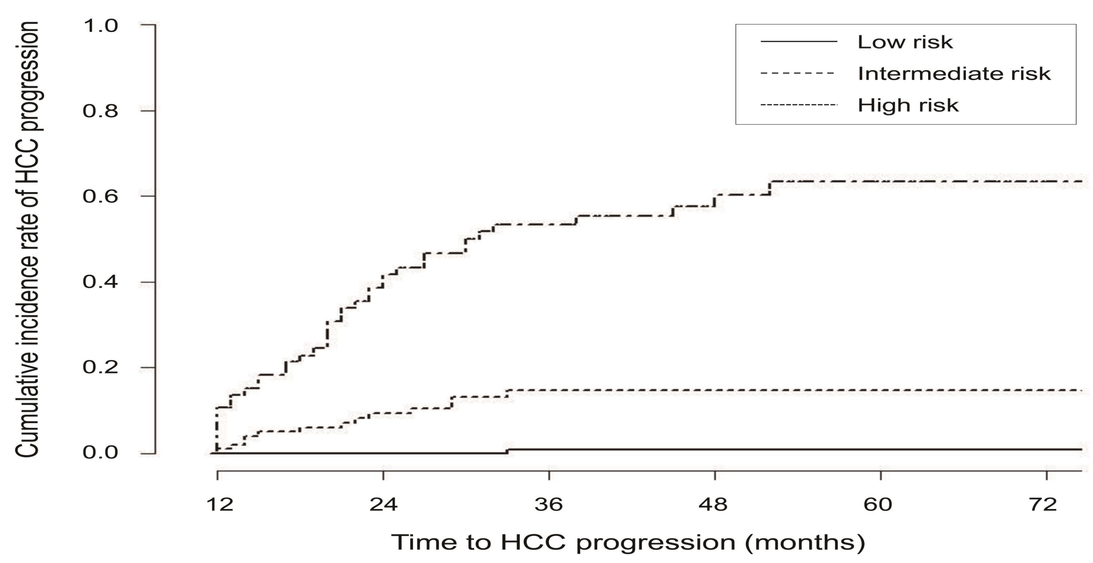
Table 4. Beta coefficient of the included risk factors identified from multivariate Cox regression analysis and their corresponding risk scores

Variables	β coefficient	HR (95% CI)	*P*	Risk score
Age, years	0.0475	1.05 (1.02-1.08)	0.0033	1
Arterial enhancement, Yes	0.8951	2.45 (1.24-4.84)	0.001	19
Nodule size, > 1cm	2.0071	7.44 (3.75-14.78)	<0.001	42
Albumin, ≤3.5 g/dL	0.7594	2.14 (1.10-4.14)	0.024	16
AFP, ≥ 100 ng/mL	1.4882	4.43 (1.38-14.17)	0.012	31
Prior HCC history, yes	1.5190	4.57 (1.93-10.81)	0.006	32
HBeAg positivity, positive	0.8320	2.30 (1.27-4.16)	0.006	18

- **Risk score = 1 x age(years) + 19 x enhancement pattern(arterial non-enhancement or AP shunt=0; arterial enhancement=1) + 42 x size(≤1cm=0;>1cm=1) + 16 x serum albumin (>3.5g/dL=0;≤3.5g/dL=1) + 31 x serum AFP(<100ng/mL=0; ≥100ng/mL=1) + 32 x prior HCC history(no=0; yes=1) + 18 x HBeAg(negative=0; positive=1)**



- Fig 2. Time-dependent ROC and calculated AUC in development cohort and leave-one-out cross-validation (a) 36 months (b) 60 months



- Fig 3. Comparison of HCC progression incidence between three groups divided by calculated risk score as low, intermediate, and high-risk groups.
- We identified patients at low (risk score<60), intermediate (60<risk score<105), and high risk (risk score>105) for HCC; 5-year cumulative incidences were 1%, 14.5%, and 63.1%, respectively.

CONCLUSION

- We developed useful and accurate risk score model for predicting HCC progression of indeterminate nodules detected on HBV-related cirrhotic liver.