SUPPLEMENTARY MATERIAL

Prediction and clinical utility of a liver cancer risk model in Chinese adults: a prospective cohort study of 0.5 million people

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Supplementary Text 1. Details of physical measurement and blood test results of the CKB-PLR (Prediction for Liver cancer Risk based on the CKB study) model.

Daily level of physical activity was calculated by multiplying the METs value for a particular type of activity by hours spent on that activity per day and summing the MET-hours for all activities. BMI was calculated as weight (kg) divided by the square of height (m²). Previous diabetes history was defined on the basis of self-reported history of diabetes. Participants with random plasma glucose (RPG) levels ≥ 7.8 and < 11.1 mmol/L were invited to have a fasting plasma glucose (FPG) test the following day. Screen-detected diabetes was defined as (i) measured random blood glucose ≥ 7.0 mmol/L and time since last eating ≥ 8 hours, or (ii) measured random blood glucose ≥ 11.1 mmol/L if the time since last eating was < 8 hours, or (iii) measured fasting blood glucose ≥ 7.0 mmol/L on subsequent testing among participants without previously diagnosed diabetes. Diabetes was defined as having either previously diagnosed diabetes or screen-detected diabetes. In addition, desktop analysers were used to measure random plasma glucose (Johnson & Johnson SureStep Plus Meter) and hepatitis B surface antigen (ACON Biotech).

Supplementary Text 2. Decision curve analysis to estimate the clinical utility of the CKB-PLR (Prediction for Liver cancer Risk based on the CKB study) model.

The decision curve analysis combines the direct applicability of the decision-analytic methods with the mathematical simplicity of accuracy metrics [1]. The mathematical background of the net benefit calculation was originally developed in 1884 [2]. More recently, other publications expanded this work and emphasize why the net benefit measures should be used beyond measures of discrimination and calibration to assess the accuracy of prediction models [3].

The net benefit (NB) is calculated as:

$$NB = \frac{TP}{n} - \frac{FP}{n} \left(\frac{p_t}{1 - p_t} \right)$$

Where n is the total sample size TP = true positive counts; FP = false positive counts; p_t = risk threshold that defines the high risk and low risk participants. The ratio $\frac{p_t}{1 - p_t}$ represents the relative weight of the harm of unnecessary liver cancer screening versus the benefit of liver cancer patients who truly need the screening. To draw the decision curve, the net benefit is calculated for different values of p_t .

The net benefit of a prediction model is traditionally compared with the strategies of treat all or treat none. Although discrimination measures such as sensitivity, specificity, and c-statistic and calibration measures cannot be used to assess the clinical utility of a prediction model, net benefit is larger for more discriminating models and decrease with poor calibration [4].

Either 'opt-in' or 'opt-out', describing the type of policy for which to report the net benefit. A policy is 'opt-in' when the standard-of-care for a population is to assign a particular screening to no one. Clinicians then use a risk model to categorize participants as 'high-risk', with the recommendation to treat high-risk participants with screening. Alternatively, an 'opt-out' policy is applicable to contexts where the standard-of-care is to recommend a screening to an entire participants. The potential use of a risk model in this setting is to identify participants who are 'low-risk' and recommend that those participants 'opt-out' of screening [5].

Supplementary Table 1. Basic characteristics of the cohort follow-up, liver cancer diagnosis and deaths in the development/validation datasets.

Dataset	Variable	Person-Years	Liver Cancers	Deaths	Liver Cancer Incidence Rate Per 100,000 person years (95% CI)*
Overall (N=486,285)	HBsAg status				
	Seronegative	4,667,556	2,019	38,635	31.59 (29.95-33.32)
	Seropositive	146,764	687	1,699	401.96 (371.64-434.76)
	Overall	4,814,320	2,706	40,334	42.89 (40.92-44.96)
Development Dataset (N=389,028)	HBsAg status				
	Seronegative	3,734,512	1,624	30,945	31.81 (29.98-33.76)
	Seropositive	117,119	549	1,357	401.45 (367.72-438.28)
	Overall	3,851,631	2,173	32,302	43.07 (40.86-45.39)
Validation Dataset (N=97,257)	HBsAg status				
	Seronegative	933,044	395	7,690	30.68 (27.19-34.63)
	Seropositive	29,645	138	342	404.15 (339.31-481.39)
	Overall	962,689	533	8,032	42.17 (37.93-46.90)

* Incidence rate for liver cancer are adjusted for age at baseline, gender, and residential area.

Supplementary Table 2. Detailed descriptions of the parameters for the hepatocellular carcinoma (HCC) risk model in HBsAg seronegative and seropositive participants in the development dataset.

Predictor	HBsAg Seronegative		HBsAg Seropositive	
	HR (95% CI)*	Beta	HR (95% CI)*	Beta
First spline basis of age (knots:30, 50, 60, 70, 80)	5.92 (5.22-6.68)	1.778	10.29 (8.42-12.47)	2.331
Second spline basis of age (knots:30, 50, 60, 70, 80)	8.78 (7.52-10.20)	2.172	2.64 (1.83-3.75)	0.971
Third spline basis of age (knots:30, 50, 60, 70, 80)	30.47 (25.51-36.24)	3.417	53.15 (40.71-68.72)	3.973
Forth spline basis of age (knots:30, 50, 60, 70, 80)	4.56 (3.60-5.78)	1.517	17.75 (12.18-26.14)	2.876
Male (vs.female)	1.90 (1.78-2.02)	0.642	2.78 (2.51-3.07)	1.022
Residential area (urban vs. rural)	0.84 (0.77-0.91)	-0.176	0.77 (0.67-0.87)	-0.263
Highest education (Middle school and higher vs. Others)	0.77 (0.70-0.83)	-0.264	0.99 (0.87-1.12)	-0.007
Family history of cancer (yes vs. no)	1.06 (0.94-1.19)	0.062	1.29 (1.09-1.52)	0.258
Previous cancer diagnosis (yes vs. no)	2.45 (1.58-3.59)	0.896	1.42 (0.51-3.06)	0.354
History of diabetes (yes vs. no)	1.23 (1.05-1.43)	0.207	1.12 (0.85-1.45)	0.114
History of cirrhosis or chronic hepatitis (yes vs. no)	5.67 (4.56-6.94)	1.735	1.88 (1.54-2.27)	0.632
History of gallstone or gallbladder disease (yes vs. no)	1.89 (1.61-2.19)	0.634	1.40 (1.03-1.85)	0.339
Body-mass index, per 1-unit increase	0.97 (0.97-0.97)	-0.029	0.98 (0.98-0.98)	-0.021
Physical activity, per 1-unit increase	0.99 (0.99-0.99)	-0.008	1.00 (0.99-1.00)	-0.004
First spline basis of random glucose (knots: 2.8, 5.6, 6.8, 11.1)	1.29 (1.20-1.39)	0.255	1.96 (1.76-2.23)	0.674
Second spline basis of random glucose (knots: 2.8, 5.6, 6.8, 11.1)	1.24 (1.12-1.37)	0.215	3.37 (2.85-3.97)	1.215
Third spline basis of random glucose (knots: 2.8, 5.6, 6.8, 11.1)	1.38 (1.28-1.47)	0.320	1.98 (1.76-2.20)	0.683
Tobacco regular consumption (smokers vs. never)	1.22 (1.13-1.31)	0.197	1.31 (1.17-1.46)	0.271
Alcohol regular consumption (drinkers vs. never)	1.39 (1.27-1.52)	0.331	1.04 (0.89-1.21)	0.042

* HR, hazard ratio. CI, confidence interval.

Supplementary Table 3. Comparison of the liver cancer classifications according to the HBsAg seropositive criteria and the CKB-PLR model*.

Criteria	Participants with Liver Cancer (N=497)	Participants without Liver Cancer (N=96760)	Predictive Value
HBsAg Seropositive[†]			
Criteria positive	129 TP (25.96%)	2940 FP (3.04%)	PPV, 4.20%
Criteria negative	368 FN (74.04%)	93820 TN (96.96%)	NPV, 99.61%
CKB-PLR[‡]			
Criteria positive	142 TP (28.57%)	2927 FP (3.03%)	PPV, 4.63%
Criteria negative	355 FN (71.43%)	93833 TN (96.97%)	NPV, 99.62%

* TP denotes true positive, FP denotes false positive, FN denotes false negative, TN denotes true negative, PPV denotes positive predictive value, and NPV denotes negative predictive value;

[†] HBsAg Seropositive criteria were defined as people with hepatitis B virus infection;

[‡] According to the CKB-PLR (Prediction for Liver cancer Risk based on the CKB study) model criteria, positivity was defined as a probability of liver cancer greater than 1.926% over a period of 10 years.

Supplementary Table 4. Net Benefit of the CKB-PLR (Prediction for Liver Cancer Risk based on the CKB Study) model. At the same probability threshold, the net benefit is exemplified in HBsAg Seronegative participants ('opt-in' policy) and HBsAg Seropositive participants ('opt-out' policy).

Probability threshold, pt (%)	Unnecessary screening needed to confirm one liver cancer*	HBsAg Seronegative	HBsAg Seropositive
		Net benefit versus treat no participants with screening (95% CI)	Net benefit versus treat all participants with screening (95% CI)
0.50	199.00	1.24E-03 (1.07E-03, 1.38E-03)	9.10E-03 (-1.91E-02, 2.41E-02)
1.00	99.00	3.82E-04 (2.78E-04, 4.79E-04)	5.80E-02 (9.43E-03, 1.06E-01)
1.50	65.67	1.11E-04 (4.89E-05, 1.76E-04)	1.01E-01 (4.78E-02, 1.47E-01)
2.00	49.00	7.74E-05 (3.02E-05, 1.23E-04)	1.63E-01 (1.16E-01, 2.04E-01)
2.50	39.00	3.78E-05 (2.39E-06, 8.07E-05)	2.11E-01 (1.62E-01, 2.53E-01)
3.00	32.33	2.49E-05 (-6.13E-06, 6.15E-05)	2.69E-01 (2.22E-01, 3.13E-01)
3.50	27.57	1.68E-05 (-1.24E-05, 4.95E-05)	3.14E-01 (2.71E-01, 3.56E-01)
4.00	24.00	1.34E-05 (-1.57E-05, 4.17E-05)	3.36E-01 (2.92E-01, 3.76E-01)
4.50	21.22	9.07E-06 (-1.81E-05, 3.72E-05)	3.66E-01 (3.26E-01, 4.04E-01)
5.00	19.00	5.70E-06 (-2.11E-05, 3.33E-05)	3.99E-01 (3.62E-01, 4.35E-01)

*The number of unnecessary screening needed to confirm a liver cancer event is calculated by $(1 - pt)/pt$.

Supplementary Table 5. Distribution of demographic characteristics and covariates of the HBsAg seronegative participants according to a probability cutoff of 2%.

Characteristics		Normal (N=466,503) No. (%)	High Risk (N=4,614) No. (%)	P value*
Gender	Female	279,059 (59.82)	679 (14.72)	<0.001
	Male	187,444 (40.18)	3,935 (85.28)	
Age at baseline (Years)	<50	213,520 (45.77)	161 (3.49)	<0.001
	50-59	144,443 (30.96)	863 (18.70)	
	60-69	80,290 (17.21)	2,328 (50.46)	
	≥70	28,250 (6.06)	1,262 (27.35)	
Residential area	Rural	258,974 (55.51)	2,455 (53.21)	0.002
	Urban	207,529 (44.49)	2,159 (46.79)	
Highest education	Primary School and lower	233,154 (49.98)	3,216 (69.70)	<0.001
	Middle school and higher	233,349 (50.02)	1,398 (30.30)	
Family history of cancer	No	386,161 (82.78)	3,583 (77.65)	<0.001
	Yes	80,342 (17.22)	1,031 (22.35)	
Previous cancer diagnosis	No	464,635 (99.60)	4,153 (90.01)	<0.001
	Yes	1,868 (0.40)	461 (9.99)	
History of diabetes	No	439,799 (94.28)	3,338 (72.35)	<0.001
	Yes	26,704 (5.72)	1,276 (27.65)	
History of cirrhosis or chronic hepatitis	No	464,536 (99.58)	2,605 (56.46)	<0.001
	Yes	1,967 (0.42)	2,009 (43.54)	
History of gallstone or gallbladder disease	No	440,045 (94.33)	2,799 (60.66)	<0.001
	Yes	26,458 (5.67)	1,815 (39.34)	
Body-mass index (kg/m²)	<18.5	19,515 (4.18)	490 (10.62)	<0.001
	18.5-23.9	240,711 (51.60)	2,486 (53.88)	
	24-27.9	156,139 (33.47)	1,324 (28.70)	
	≥28	50,138 (10.75)	314 (6.81)	
Random plasma glucose (mmol/L)	<5.6	227,476 (48.76)	1,422 (30.82)	<0.001
	5.6-6.7	149,575 (32.06)	1,090 (23.62)	
	6.8-7.7	49,135 (10.53)	596 (12.92)	
	7.8-11.0	26,923 (5.77)	659 (14.28)	
	≥11.1	13,394 (2.87)	847 (18.36)	
Physical activity (MET-hours/day)	<10.32	114,803 (24.61)	2,660 (57.65)	<0.001
	10.32-17.46	117,362 (25.16)	952 (20.63)	
	17.47-30.00	117,280 (25.14)	621 (13.46)	
	≥30.01-	117,058 (25.09)	381 (8.26)	
Tobacco smoking	Never	318,972 (68.38)	1,213 (26.29)	<0.001
	Smoker	147,531 (31.62)	3,401 (73.71)	
Alcohol drinking	Never	380,840 (81.64)	2,054 (44.52)	<0.001
	Drinker	85,663 (18.36)	2,560 (55.48)	

* Two-sided Chi-square test.

Supplementary Figure 1. Flowchart for the study design.

Supplementary Figure 2. Nonlinear Relationship between Age (A)/ Random plasma glucose (B) and Liver cancer risk. Hazards ratio between age and liver cancer risk were calculated adjusting for gender, residential area, family history of cancer, personal history of cancer, personal history of diabetes, BMI, HBsAg status, physical activity, tobacco smoking, alcohol drinking; Hazards ratio between random plasma glucose levels and liver cancer risk were adjusted for age at baseline, gender, residential area, family history of cancer, personal history of cancer, BMI, HBsAg status, physical activity, tobacco smoking, alcohol drinking.

Supplementary Figure 3. Calibration of the CKB-PLR (Prediction for Liver cancer Risk based on the CKB study) model (A) and receiver operating characteristic curve (B) in the development dataset. (A) The observed 10-year probability and 95% confidence intervals of liver cancer were estimated with Kaplan-Meier by tenths of model-predicted probability. **(B)** The receiver operating characteristic curve corresponding to concordance (c)-statistic of 0.80 (95%CI, 0.79-0.81).

Supplementary Figure 4. The calibration and discrimination of the hepatocellular carcinoma (HCC) risk model in the validation dataset.

(A) The observed 10-year probability of HCC was estimated by the Kaplan-Meier method within a tenth of the model-predicted probability. **(B)** Receiver operating characteristic curve (concordance (c)-statistic: 0.80, 95% CI: 0.78-0.82). **(C)** Sensitivity and specificity on the basis of the predicted probability cutoff.

Supplementary Figure 5. Distribution of predicted probabilities by HBsAg Seropositive eligibility. The yellow dashed line indicates a probability cutoff of 1.926%, which yields equal participants to match the HBsAg seropositive criteria when applied to the validation dataset.

Supplementary Figure 6. Decision curve analysis for the CKB-PLR (Prediction for Liver Cancer Risk based on the CKB Study) model. (A) The decision curve 'opt-in' policy (Supplementary Text 2) to determine the net benefits of using the CKB-PLR model among participants with HBsAg seronegative (blue line) compared to treating no HBsAg seronegative participants with liver cancer screening (black solid line). (B) The decision curve 'opt-out' policy (Supplementary Text 2) to determine the net benefits of using the CKB-PLR model among participants with HBsAg seropositive (blue line) compared to treat all HBsAg seropositive participants with screening (gray solid line).

Supplementary references

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