Development and Validation of a Noninvasive Risk Score Model for Liver Cirrhosis in At-Risk Alcohol Drinkers Without HBV/HCV Infection

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ABSTRACT

At-risk alcohol consumption is the established most important risk factor for cirrhosis in people without HBV/HCV infection. We aimed to develop and validate a simple and non-invasive tool for triaging cirrhosis risk in at-risk alcohol drinkers without HBV/HCV infection. A large-sample size, cross-sectional study within the framework of a population-based Cancer Screening Program in Urban China (CanSPUC) was conducted. Data on the liver cancer screening in Henan province, China were used. At-risk alcohol drinkers were those who currently drink one or more alcohol units per week for at least six months. A total of 6,581 eligible participants enrolled from October 1, 2013 to December 31, 2016 were included into the derivation dataset, and 2,096 eligible participants enrolled from January 1, 2017 to October 31, 2018 were included into the external validation dataset, respectively. Using the derivation dataset, a 20-point scale risk score model was developed, based on sex, education background, dietary intake of vegetables, dietary intake of roughage, smoking index, length of secondhand smoke exposure, history of fatty liver, history of diabetes, and first-degree family history of liver cancer. The model showed excellent discrimination (AUC = 0.787; 95% CI, 0.7603–0.812) and calibration (Hosmer–Lemeshow test: $P = 0.123$) in the derivation dataset and an optimal cut-off value of 12 yield sensitivity of 61.3%, specificity of 82.7%. The model also had achieved similar performance in the external validation dataset. In conclusion, this model can be a practical tool to identify and triage population at high risk of cirrhosis in at-risk alcohol drinkers without HBV/HCV infection.

Prevention Relevance: The risk model we developed will not only be used as a practical tool to triage high risk groups for liver cirrhosis, but also have implications for public health measures, such as guidelines for the prevention of liver cancer, in at-risk alcohol drinkers without HBV/HCV infection.

Introduction

Liver cirrhosis is a common chronic liver disease and will eventually develop liver cancer or end-stage liver disease without treatment (1). Globally, cirrhosis causes approximately 2 million deaths, accounting for 3.5% of all deaths worldwide (2). Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most causes of liver cirrhosis and affect an estimated 325 million people worldwide (3). However, the prevalence of HBV infection has been decreasing with the implementation of universal vaccination of newborns for HBV (4), and HCV can be eradicated with the development of effective direct antivirals (5). Hence, HBV- or HCV-related liver cirrhosis is expected to decrease worldwide. On the contrary, the burden of liver cirrhosis is evolving (6). Considering this, the magnitude of cirrhosis risk for the individuals without HBV/HCV infection should be determined.

At-risk alcohol consumption, such as current consumption or heavy alcohol use over time is the established most important risk factor for cirrhosis in people without HBV/HCV infection (7–9). According to the Global status report on alcohol and health 2018 (9), total alcohol per capita consumption in the world's population over 15 years of age rose from 5.5 liters of pure alcohol in 2005 to 6.4 liters in 2010 and was still at the level of 6.4 liters in 2016. It was estimated that about half of liver cirrhosis burden of morbidity and mortality would disappear in the world without alcohol. In response, prevention and management of alcohol induced cirrhosis is of great significance to the whole world. However, it is not practical and cost-effective to screen or monitor all drinkers, despite that screening and close surveillance can prevent the development of cirrhosis (10). Therefore, risk stratification will allow us to triage and screen people with high risk, so that medical supports could be appropriately allocated.

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Cancer Prev Res 2022;15:767–76

doi: 10.1158/1940-6207.CAPR-22-0234

Liver biopsy is the standard method for the assessment of cirrhosis (11), but it is costly, invasive, and has a small but not negligible rate of complications with 0.3%–0.8% (12–16). In recent years, many studies have been done to develop alternative noninvasive models to identify and stratify cirrhosis risk. However, most of the existing models were developed in HBV or HCV infected population (17–21). To date, only one gene-based risk score model was developed for male at-risk drinkers (22). But this model did not exclude people who were infected with HBV/HCV as well as not applied to female drinkers. In addition, this model was developed on the basis of genetic factors, which could only be obtained by sophisticated laboratory testing. The cost will lead to limited availability, and the results cannot be immediately available to patients, especially in resource-limited areas. It would be ideal to develop a simple tool, using widely available and noninvasive variables without involving expensive or complicated procedures, to determine cirrhosis risk for alcohol drinkers in routine clinical practice.

Therefore, in this study, we aimed to develop and validate a simple noninvasive model to determine cirrhosis risk in at-risk alcohol drinkers without HBV/HCV infection. Such model will be easy-to-performing and clinically useful to triage drinkers, facilitate cirrhosis prevention and management, and allow targeted interventions of the individuals.

Materials and Methods

Data source and participants

This cross-sectional study was conducted within the framework of CanSPUC, an ongoing, nationwide, population-based cancer screening program in urban China. The detailed methodology of the CanSPUC has been previously described (23–26). In brief, all eligible participants (40–74 years old) who had signed a written informed consent were enrolled and interviewed by trained staffs to collect data on their exposure to risk factors of cancer. The study conformed to the guidelines explained in the Declaration of Helsinki, and was reviewed and approved by Ethics Committee of National Cancer Centre/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College.

In Henan province, CanSPUC has been launched since October 2013, covering eight cities (Zhengzhou, Zhumadian, Anyang, Luoyang, Nanyang, Jiaozuo, Puyang, and Xinxiang; ref. 24). In this study, data of the first five years (from October 2013 to October 2018) on the liver cancer screening in Henan province was used. Only those at-risk alcohol drinkers defined as currently drink one or more alcohol units per week for at least six months, were included in this study. One unit of alcohol was defined as 12 g of ethanol. Participants would be excluded if they were (i) ever infected with HBV or HCV; (ii) diagnosed with liver cancer. HBV infection was defined as HBsAg and/or HBV DNA positive, HCV infection was defined as anti-HCV positive. In this study, participants enrolled from October 1, 2013 to December 31, 2016 were included into the derivation dataset, and those enrolled from January 1, 2017 to October 31, 2018 were included into the external validation dataset. Flowchart for the recruitment of study participants was shown as **Fig. 1**.

Outcome, variables and measurements

The primary outcome was liver cirrhosis. Cirrhosis was diagnosed through B-mode ultrasound suggesting that liver capsule is wavy, cirrhotic, uneven, or ascites with no other cause explained (27).

The following data were collected through self-report, in order to identify potential risk factors for cirrhosis:

(i) Demographic characteristics: age, sex, height, weight and level of education (Low level: middle school or below; High-level: senior high school certificate or above). Body mass index (BMI) was calculated and classified as "<18.5 kg/m^2", "18.5∼23.9 kg/m^2", "24.0∼27.9 kg/m^2" and "≥28.0 kg/m^2", according to Working Group for Obesity in China (WGOC) criteria (28).

(ii) Dietary habits in the past two years. Food frequency questionnaire was used to collect dietary information, including vegetables intake (<2.5 kg/week, ≥2.5 kg/week), fruit intake (<1.25 kg/week, ≥1.25 kg/week), roughage intake (<0.5 kg/week, ≥0.5 kg/week). Food weight was determined before cooking. Taste preferences including heavy-salt diet (yes, no) and heavy-grease diet (yes, no) were also collected. Participants who reported to prefer or often eat salty and greasy food, were considered to have heavy-salt diet and heavy-grease diet, respectively.

(iii) Living environment, behavior and habits:

(a) Cooking oil fume exposure: it is considered as "None or a little", if chimneys, fume extractors, or smoke-less pots was used during cooking; otherwise, it is considered as "a lot".

(b) Smoking index: calculated by multiplying the year of smoking by the number of cigarettes per day (cigarettes/day*year), and classified as "0", "1–399" and "≥400".

(c) Length of secondhand smoke exposure (years): if the participants reported that someone often smoke in the indoor environment where they live and/or work, they were considered to be "exposed to secondhand smoke", otherwise, were considered to be "not exposed to secondhand smoke". For those participants considered to be "exposed to secondhand smoke", the length of exposure was further collected; for those participants considered to be "not exposed to secondhand smoke", the length of exposure was recoded as "0".

(d) Physical activity: participants who did exercise for at least three days with a total time ≥90 mins per week were categorized as "heavy physical activity"; otherwise, were categorized as "moderate or no physical activity".

(iv) Psychology and emotions: including history of a major trauma and history of mental depression for over 6 months.

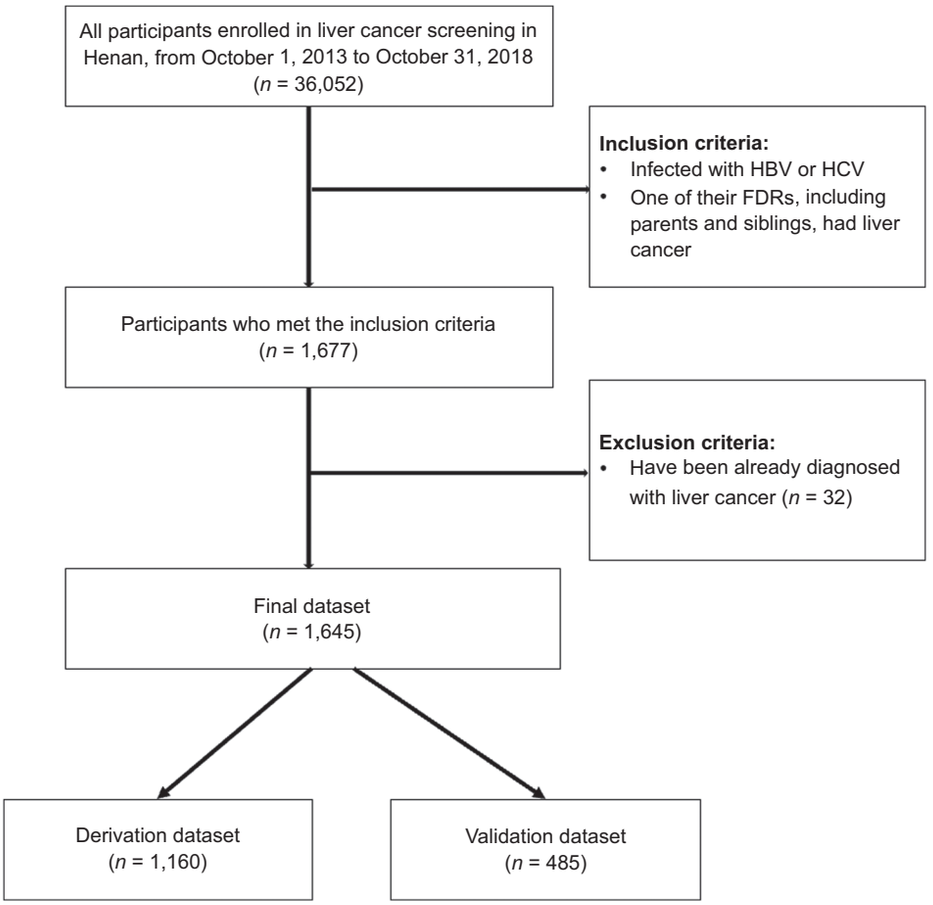

Figure 1.
Flowchart for the recruitment of study participants. A total of 6,581 eligible participants enrolled from October 1, 2013 to December 31, 2016 were included into the derivation dataset, and 2,096 eligible participants enrolled from January 1, 2017 to October 31, 2018 were included into the external validation dataset.

(v) Comorbidities: including history of fatty liver, hypertension, diabetes, and hyperlipidemia. All self-reported comorbidities were required a diagnosis from professional medical institutions.
(vi) First-degree family history of liver cancer: whether parents or siblings had liver cancer or not.

Data acquisition and quality assurance

Trained staffs and physicians collected data using standardized paper documents, checked the validity of documents and then entered the data into management system. Inconsistency of data was resolved by retrieving original records. A unique identifier was given to each participant in order to track relevant document forms. All data were transferred to the central data management team, who were responsible for data management and data analyses.

Statistical analysis

Development of risk score model

The model development and validation were performed and reported following the TRIPOD guidelines (29). To determine independent risk factors for liver cirrhosis, we applied univariate and multivariate binary logistic regression. Variables with large quantities of missing data (>20%) were not included into the multivariate model, in order to maximize sample size. Variables having a P value < 0.1 in univariate logistic regression were candidates for multivariate regression analysis. A sequential series of multivariate regression models were developed using the derivation dataset. The improvement of the model is evaluated by net reclassification improvement (NRI) and integrated discrimination index (IDI) when adding variables to the model.

The variables in the multivariate regression model were determined through step-wise use of Akaike information criterion (AIC). Each variable in the final multivariate model with the lowest AIC was assigned an integer score, by dividing corresponding β-coefficient by the significant lowest β-coefficient (30). The sum of the integers was the total score for each participant.

Performance of risk score model and internal validation

Performance of the risk score model was evaluated using discrimination, calibration, risk classification ability, and clinical usefulness.

The discrimination of the model was evaluated by the receiver operating characteristic (ROC) with AUC. To evaluate calibration of the model, Hosmer–Lemeshow goodness of fit

tests were conducted with a $P > 0.05$ considered as fair calibration. Sensitivity, specificity, and predictive values were calculated to measure the risk classification ability of this model. Two cut-off points of the risk score were selected and used to category the population into 3 groups: low-risk, medium-risk, and high-risk. One point was the optimal cut-off point with the optimal value both sensitivity and specificity, another point was selected according to the risk score distribution and adjusted with consideration for the convenience of clinical adoption. To evaluate the performance of each category for predicting the risk of cirrhosis, ORs were calculated using the low-risk group as the reference group. To evaluate the clinical usefulness of the risk score model, decision curve analysis (DCA) was assessed by quantifying the net benefits at different threshold probabilities.

The risk score model was internally validated through bootstrap resampling, in order to address overfitting and quantify optimism. Optimism is the difference between the unadjusted AUC and bootstrap (bias-) corrected AUC (31). Bias-corrected AUC was calculated using 1,000 bootstrap resamples.

External validation of risk score model

The risk score model developed using the derivation dataset was applied on the external validation dataset. The performance of the risk model was evaluated as in the derivation dataset.

All statistical analyses were conducted using R Project for Statistical Computing (https://www.r-project.org/ 4.1.3). Descriptive statistics were used to present data. Mean and SD were used for normally continuous variables, median and first-quantile (Q1) and third-quantile (Q3) were used for nonnormally continuous variables, frequency distributions and percentages were used for categorical variables. Difference between the derivation and validation dataset was tested using Student *t* test for normally continuous variable, Wilcoxon test for nonnormally continuous variables, and χ^2 test for categorical variable. Two-sided $P < 0.05$ was considered as statistically significant.

Data availability statement

The data generated in this study are available upon request from the corresponding author.

Results

Characteristics of study participants

A total of 8,677 eligible participants were included in this study. The derivation dataset included 6,581 participants and the external validation dataset included 2,096 participants. The characteristics of the derivation and external validation datasets were shown in Supplementary Table S1 in the supplement. Participants in the derivation dataset had higher education level, lower frequency of roughage intake, higher proportion of heavy-salt diet, higher proportion of heavy-grease diet, lower proportion of cooking oil fume exposure, lower length of secondhand smoke exposure, lower proportion of a major trauma history, lower proportion of fatty liver history, higher proportion of hyperlipidemia history, higher proportion of diabetes history, lower proportion of first-degree family history of liver cancer. About 4.2% (279/6,581) and 3.8% (79/2,096) participants suffered from liver cirrhosis in the derivation and external validation dataset, respectively.

Development of risk score model

The univariate logistic regression was performed for every eligible variable in the derivation dataset, as shown in **Table 1**. Five multivariate models were conducted as shown in Supplementary Table S2. Model 5 was the final multivariate regression model with the lowest AIC of 184.01. The NRI and IDI of the Model 5 were 0.564 [95% confidence interval (CI), 0.451–0.676] and 0.023 (95% CI, 0.018–0.027), respectively, compared with Model 1, suggesting the net reclassification was significantly improved.

In the final model, being female (AOR = 2.03; 95% CI, 1.46–2.83), low-level education (AOR = 1.30; 95% CI, 1.01–1.66), dietary intake of vegetables<2.5 kg/week (AOR = 1.86; 95% CI, 1.33–2.59), dietary intake of roughage<0.5 kg/week (AOR = 1.40; 95% CI, 1.08–1.81), smoking (index of 1–399: AOR = 2.40; 95% CI, 1.57–3.66; index ≥400: AOR = 3.41; 95% CI, 2.73–5.12), high length of secondhand smoke exposure (1–29: AOR = 1.29; 95% CI, 0.85–1.94; ≥30: AOR = 1.97; 95% CI, 1.32–2.95), history of fatty liver (AOR = 1.69; 95% CI, 1.24–2.30), history of diabetes (AOR = 1.72; 95% CI, 1.21–2.44), and first-degree family history of liver cancer (AOR = 1.36; 95% CI, 1.04–1.78) were independent risk factors of liver cirrhosis. Using these nine variables, a 20-point scale cirrhosis risk score model was developed, as shown in **Table 2**.

Performance of risk score model and internal validation

The risk score model achieved an excellent discriminatory performance with an AUC of 0.787 (95% CI, 0.7603–0.812) in the derivation dataset. After bootstrap internal validation, bias-corrected AUC was 0.771 (95% CI, 0.760–0.802), indicating minimal overfitting of the risk score model to the data. (**Fig. 2**). The model achieved a Hosmer–Lemeshow statistic of 11.37 ($P = 0.123$), suggesting fair calibration.

As shown in **Table 3**, the optimal cut-off point was 12 with sensitivity of 61.3% (95% CI, 58.4%-66.2%), specificity of 82.7% (95% CI, 81.9%–83.5%), positive predictive value (PPV) of 24.4% (95% CI, 22.4%–26.3%), and negative predictive value (NPV) of 96.1% (95% CI, 95.5%–96.5%). We divided the participants into three groups: low-risk group (0–7 points), medium-risk group (8–12 points), and high-risk group (13–20 points). Compared with participants in the low-risk group, participants in the medium- (OR = 2.10; 95% CI, 1.50–2.94) and high-risk groups (OR = 7.43; 95% CI, 5.09–10.84) had higher proportions of liver cirrhosis (**Table 4**).

The DCA showed that when the threshold probability was within a range of 3.0% to 20.0%, using the risk score model to

Table 1. Univariate analysis of risk factors for liver cirrhosis in the derivation dataset.

Variables	No cirrhosis ($n = 6,302$)	Cirrhosis ($n = 279$)	OR (95% CI)	*P*
Demographic characteristics			—	
Age			—	
$\bar{x} \pm s$	54.4 ± 8.13	54.9 ± 7.39	1.01 (0.99–1.02)	0.315
Sex				
Male	4,953 (96.2)	198 (3.8)	Reference	
Female	1,349 (94.3)	81 (5.7)	1.50 (1.15–1.95)	0.003
BMI (kg/m^2)				
<18.5	54 (96.4)	2 (3.6)	Reference	
18.5∼23.9	2,124 (94.7)	118 (5.3)	1.50 (0.36–6.20)	0.577
24.0∼27.9	3,096 (96.2)	121 (3.8)	1.06 (0.25–4.37)	0.941
≥28.0	1,028 (96.4)	38 (3.6)	1.00 (0.23–4.24)	0.998
Level of education				
Low level	2,570 (95.2)	130 (4.8)	1.27 (1.00–1.61)	0.050
High level	3,732 (96.2)	149 (3.8)	Reference	
Dietary habit in the past two years				
Vegetables intake				
≥2.5kg/week	1,861 (97.6)	46 (2.4)	Reference	
<2.5kg/week	4,441 (95.0)	233 (5.0)	2.12 (1.54–2.92)	<0.001
Fruit intake				
≥1.25kg/week	1,307 (96.8)	43 (3.2)	Reference	
<1.25kg/week	4,995 (95.5)	236 (4.5)	1.44 (1.03–1.99)	0.032
Roughage intake				
≥0.5kg/week.	1,307 (97.2)	38 (2.8)	Reference	
<0.5kg/week	4,995 (95.4)	241 (4.6)	1.66 (1.17–2.34)	0.004
Heavy-salt diet				
No	2,704 (95.9)	117 (4.1)	Reference	
Yes	3,598 (95.7)	162 (4.3)	1.04 (0.81–1.32)	0.749
Heavy-grease diet				
No	4,191 (96.2)	167 (3.8)	Reference	
Yes	2,111 (95.0)	112 (5.0)	1.33 (1.04–1.70)	0.022
Living environment, behavior, and habits				
Cooking oil fume exposure				
None or a little	3,586 (96.6)	127 (3.4)	Reference	
A lot	2,716 (94.7)	152 (5.3)	1.58 (1.24–2.01)	<0.001
Smoking index (cigarettes/day/year)				
0	1,695 (97.5)	44 (2.5)	Reference	
1–399	3,153 (95.6)	145 (4.4)	1.77 (1.2–2.49)	0.001
≥400	1,454 (94.2)	90 (5.8)	2.38 (1.6–3.44)	<0.0001
Length of secondhand smoke exposure (years)[a]				
0	1,529 (97.8)	34 (2.2)	Reference	
1–29	2,402 (96.1)	97 (3.9)	1.82 (1.22–2.69)	0.003
≥30	2,371 (94.1)	148 (5.9)	2.81 (1.92–4.09)	<0.0001
Physical activity			—	
Moderate or No	4,265 (95.2)	214 (4.8)	Reference	
Heavy	2,037 (96.9)	65 (3.1)	0.64 (0.40–0.84)	0.002
Psychology and emotions				
History of a major trauma				
No	3,601 (96.0)	150 (4.0)	Reference	
Yes	2,701 (95.4)	129 (4.6)	1.15 (0.90–1.45)	0.265
Mental depression for over 6 months				
No	3,151 (95.7)	141 (4.3)	Reference	
Yes	3,151 (95.8)	138 (4.2)	0.98 (0.70–1.24)	0.861
Comorbidities				
Fatty liver[b]				
Missing	201 (100.0)	0 (0.0)		
No	1,582 (97.5)	40 (2.5)	Reference	
Yes	4,519 (95.0)	239 (5.0)	2.09 (1.49–2.94)	<0.001
Hypertension				
No	3,840 (96.0)	159 (4.0)	Reference	
Yes	2,462 (95.4)	120 (4.6)	1.18 (0.92–1.49)	0.187

(Continued on the following page)

Table 1. Univariate analysis of risk factors for liver cirrhosis in the derivation dataset. (Cont'd)

Variables	No cirrhosis ($n = 6,302$)	Cirrhosis ($n = 279$)	OR (95% CI)	*P*
Hyperlipidemia				
No	3,485 (96.0)	147 (4.0)	Reference	
Yes	2,817 (95.5)	132 (4.5)	1.11 (0.87–1.40)	0.391
Diabetes				
No	5,510 (96.1)	223 (3.9)	Reference	
Yes	792 (93.4)	56 (6.6)	1.75 (1.29–2.36)	<0.001
First-degree family history of liver cancer				
No	4,860 (96.1)	199 (3.9)	Reference	
Yes	1,442 (94.7)	80 (5.3)	1.36 (1.03–1.76)	0.025

[a]Classified as "0", "1–29", and "≥30", according to the median (30 years) length of secondhand smoke exposure of people who were "exposed to secondhand smoke".
[b]Numbers of the variable of fatty liver were 6,380 not 6,581, due to missing values.

triage drinkers who should be tested for liver cirrhosis would provide greater benefit than all-screening or nonscreening scenarios (**Fig. 3**).

External validation of risk score model

The model achieved an excellent discrimination in the external validation dataset, with an AUC of 0.804 (95% CI, 0.783–0.825; **Fig. 2**). The Hosmer–Lemeshow statistic was 4.55 ($P = 0.715$), indicating good agreement between the observed and predicted risk in the validation dataset.

The optimal cut-off point was 12 with sensitivity of 58.3% (95% CI, 54.2%–62.3%), specificity of 89.1% (95% CI, 88.4%–89.9%), PPV of 31.7% (95% CI, 28.9%–34.4%), and NPV of 96.0% (95% CI, 95.8%–96.5%; **Table 3**). Compared with participants in the low-risk group, participants in the medium- (OR = 2.33; 95% CI, 1.39–3.91) and high-risk groups (OR = 6.02; 95% CI, 3.30–10.99) had higher proportions of liver cirrhosis (**Table 4**).

The DCA showed that when the threshold probability was within a range of 3.0% to 20.0%, the benefit of the risk score model was higher than the extreme curve, indicating that the model had good clinical utility (**Fig. 3**).

Discussion

In this study, we developed and validated a scoring assessment model for cirrhosis in at-risk alcohol drinkers without HBV/HCV infection, based on nine widely available variables, including demographics (sex, level of education), dietary intake of vegetables, dietary intake of roughage, smoking index, length of secondhand smoke exposure, comorbidities (fatty liver, diabetes) and first-degree family history of liver cancer. The model score ranges from 0 to 20 points where higher scores indicate higher risk of cirrhosis and hence a greater need for cirrhosis screening, closer follow-up, and aggressive medical supports.

The model showed an excellent discrimination both in the derivation and validation sets. At an optimal cut-off of 12 point, the specificity was above 80% and the NPV was above 96%, while the sensitivity was only about 60% and the PPV was about 25%. This result suggested that this model would be a powerful aid in triaging patients and reducing over screening, but not a good tool for early detection of cirrhosis. However, knowledge of the cirrhosis risk and risk stratification could help to promote the primary prevention of cirrhosis, improve the screening awareness of high-risk alcohol drinkers without HBV/HCV infection, and ultimately facilitate the early detection of cirrhosis.

The DCA was widely used to evaluate the clinical usefulness of risk score model. In the study, DCA determined that the clinical net benefit of the model we developed was larger than that in the hypothetical all-screening or non-screening scenarios, with a wide range threshold of 3.0% to 20.0%. Previous studies suggested that about 10% of at-risk alcohol drinkers will develop cirrhosis (32–34), and our study suggested that about 4% of at-risk alcohol drinkers without HBV/HCV had cirrhosis. Therefore, our risk score model could be a useful clinical tool to estimate the risks of liver cirrhosis and provide an avenue for targeted screening identified the drinkers with a high risk of liver cirrhosis.

Cigarette smoking is a significant health threat for smokers and nonsmokers. In our study, smoking and secondhand smoke were the strongest indicators of cirrhosis in at-risk alcohol drinkers without HBV/HCV infection. Previous studies revealed that smoking could damage the antioxidant system and then increase the risk of cirrhosis (35, 36). Our study further suggested that the risk of cirrhosis increased as the smoking index raised, and the safety index appeared to be zero. The accumulation of secondhand smoke will lead to increased lipid levels, a potential contributor to cirrhosis (37). Our study also confirmed that the risk of cirrhosis in at-risk alcohol drinkers without HBV/HCV infection was positively related with the length of secondhand smoke exposure, especially in people exposed for above 30 years. Therefore, timely smoking cessation education should be provided and smoke free housing policies are urgently strengthened as primary prevention strategy for liver cirrhosis.

Many studies have proved that females were more susceptible to alcoholic cirrhosis (38, 39). Similarly, we also found females had a higher risk of cirrhosis. Therefore, more abstinence interventions and screening for cirrhosis should be implemented among female drinkers. Different to other studies (33, 40–42), we did not find significant association

Table 2. Variables in the final multivariate logistic regression model and score assigned.

	AOR (95% CI)	β coefficient	Score assigned[a]
Sex			
Male	Reference	Reference	0
Female	2.03 (1.46–2.83)	0.71	3
Level of education			
Low level	1.30 (1.01–1.66)	0.26	1
High level	Reference	Reference	0
Dietary intake of vegetables			
≥2.5 kg/week	Reference	Reference	0
<2.5 kg/week	1.86 (1.33–2.59)	0.62	2
Roughage intake			
≥0.5 kg/week.	Reference	Reference	0
<0.5 kg/week	1.40 (1.08–1.81)	0.33	1
Smoking index (cigarettes/day/year)			
0	Reference	Reference	0
1–399	2.40 (1.57–3.66)	0.87	3
≥400	3.41 (2.73–5.12)	1.23	5
Length of secondhand smoke exposure (years)			
0	Reference	Reference	
1–29	1.29 (0.85–1.94)	0.25	0
≥30	1.97 (1.32–2.95)	0.68	3
Fatty liver			
No	Reference	Reference	0
Yes	1.69 (1.24–2.30)	0.52	2
Diabetes			
No	Reference	Reference	0
Yes	1.72 (1.21–2.44)	0.54	2
First-degree family history of liver cancer			
No	Reference	Reference	0
Yes	1.36 (1.04–1.78)	0.31	1

Abbreviation: AOR, Adjusted OR.

[a]The score was assigned by dividing corresponding β-coefficient by the significant lowest β-coefficient, rounding to the nearest integer. For example, the score of "female" was assigned through dividing 0.71 by 0.26 and taking an integer.

between BMI or obesity and cirrhosis. The reason may be that this study was cross-sectional so that the time sequence between BMI or obesity and cirrhosis could not be determined. Many obese patients had lost weight after having cirrhosis, due to that cirrhosis could cause the decline of anabolism, the rise of consumption metabolism (43). However, we found fatty liver and diabetes were independent risk factors for cirrhosis, which might provide an indirect evidence that high BMI or obesity was associated with cirrhosis (44–47). Therefore, healthy diet and prevention of obesity should be strengthened, to reduce the incidence of cirrhosis. Interestingly, we further found that eating more vegetables and roughage was associated with decreased risk of cirrhosis among at-risk alcohol drinkers without HBV/HCV infection. Vegetarian and fiber diet can reduce insulin resistance and reduce body weight (48, 49), so it potentially prevents the occurrence of fatty liver and obesity as well as reduces the progression of liver fibrosis.

In this study, drinkers with first-degree family history of liver cancer were more likely to have cirrhosis. This finding provides an evidence that genetic and environmental factors interact to cause liver damage. Further collection of detailed information about liver damage in first-degree relatives, such as the age and prognosis of cirrhosis or liver cancer, is needed to determine the impact of interactions of gene-environmental factors on cirrhosis.

Data are lacking on the association between education level and cirrhosis. We found drinkers with a low education level were more likely to have cirrhosis. A low education level may be not a risk factor itself, but it can be an indirect indicator of risky behaviors and habits. Additionally, patients with low education level are related to low socio-economic status and have limited access to medical care (50, 51), which may aggravate the liver injury. Thus, it is important to improve public awareness of alcohol hazards, strengthen health education of liver damage, and facilitate the access to medical care.

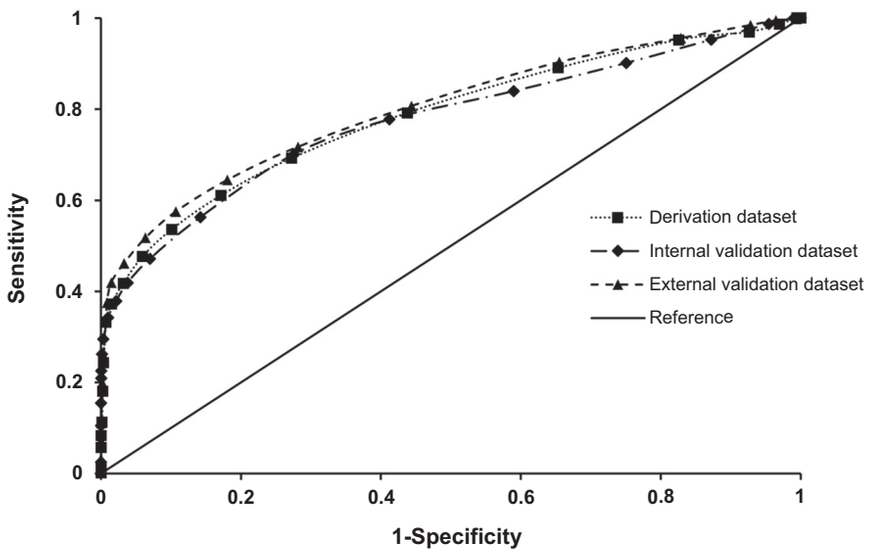

Figure 2.
The receiver operating characteristic (ROC) with AUC for both the derivation and validation dataset. The AUC was 0.787 (95% CI, 0.7603–0.812), 0.771 (95% CI, 0.760–0.802), and 0.804 (95% CI, 0.783–0.825) in derivation, internal validation and external validation dataset, respectively. CI, confidence interval.

Table 3. Distribution of risk group and corresponding sensitivity, specificity, and predictive values when categorized at different cut-off points.

Risk category	*n* (%)	Prevalence (%)	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	PPV (95% CI) (%)	NPV (95% CI) (%)
Derivation dataset						
Low-risk group (score 0–7)	2,236 (34.0)	2.0				
Medium-risk group (score 8–12)	3,748 (56.9)	4.1	61.3 (58.4–66.2)	82.7 (81.9- 83.5)	24.4 (22.4–26.3)	96.1 (95.5–96.5)
High-risk group (score 13–20)	597 (9.1)	13.2	33.3 (29.7–37.2)	99.2 (99.0–99.4)	79.5 (74.1–84.1)	94.4 (93.9–94.9)
External validation dataset						
Low-risk group (score 0–7)	902 (35.1)	2.1				
Medium-risk group (score 8–12)	1,423 (55.4)	4.8	58.3 (54.2–62.3)	89.1 (88.4–89.9)	31.7 (28.9–34.4)	96.0 (95.8–96.5)
High-risk group (score 13–20)	244 (9.5)	11.5	25.9 (22.4–29.7)	99.6 (99.5–99.8)	85.5 (79.3–90.1)	94.3 (93.7–94.8)

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

Table 4. The ORs in the medium- and high-risk groups compared with the low-risk group.

	Derivation dataset		External validation dataset	
Risk group	OR (95% CI)	*P*	OR (95% CI)	*P*
Low-risk group (score 0–7)	Reference		Reference	
Medium-risk group (score 8–12)	2.10 (1.50–2.94)	<0.001	2.33 (1.39–3.91)	0.001
High-risk group (score 13–20)	7.43 (5.09–10.84)	<0.001	6.02 (3.30–10.99)	<0.001

To our knowledge, this is a simple risk score model for liver cirrhosis in at-risk alcohol drinkers without HBV/HCV infection, using large population-based survey data. The variables included in this model could be easily collected and updated without any imaging, sophisticated testing or calculation. Moreover, the model will not only be used as a practical tool to triage high-risk patients, but also have implications for public health measures, such as guidelines for the prevention of cirrhosis.

There were several limitations in this study. First, previous studies suggested that alcohol drinking pattern, such as alcohol amount, drinking frequency and beverage type, was associated with the risk of liver cirrhosis. Since the data was second-hand from the CanSPUC database, we did not have detailed information on the pattern of alcohol consumption. But the rate of cirrhosis in our population was consistent with previous reports (34) and our model had good performance, suggesting the results were reliable and could be applicable to all alcohol drinkers without HBV/HCV infection. Second, since this study was cross-sectional, the causal relationship between risk factors and cirrhosis could not be determined. Third, the self-report data might be subjected to recall biases and social desirability.

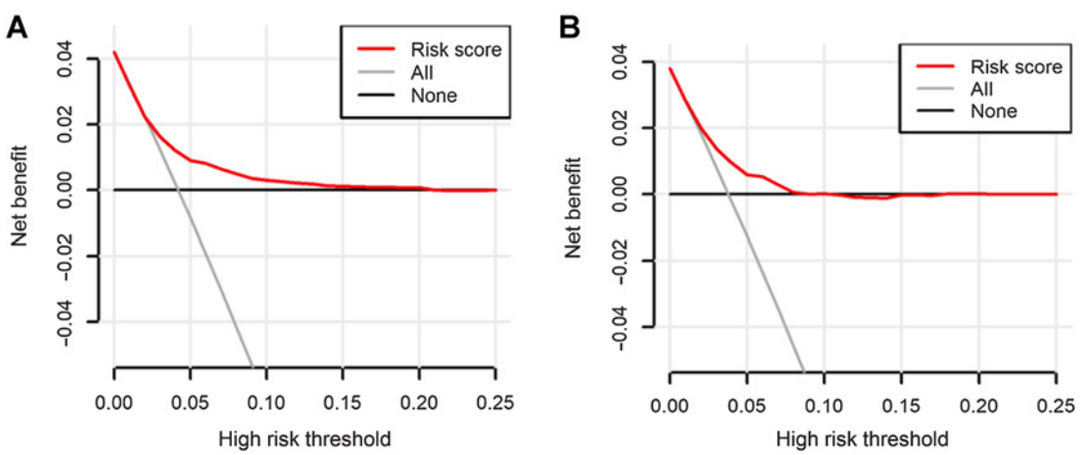

Figure 3.

Decision curve analysis (DCA) for the risk score model. **A,** DCA for the derivation dataset; (**B**) DCA for the validation dataset. The *y*-axis measures the net benefit and the *x*-axis shows the threshold probability. The horizontal black line along the *x*-axis represents the assumption that screening none ("None"), whereas the solid gray line represents the assumption that screening all ("All").

However, given the good data acquisition and quality control, most information is believed to be reliable. Fourth, the measurement of some variables was not accurate and objective. For example, heavy-salt diet and heavy-grease diet were defined according to participants' taste preferences, rather than the specific amount of salt and oil consumed by participants. Lastly, this study was conducted in a single province, and the external validation dataset basically seems similar to the derivation dataset. It might limit the application of this model to populations in other regions or provinces. Further research is needed to validate the model in other regions. Prospective validation studies will also be important.

Conclusions

In conclusion, we confirmed that being female, low-level education, dietary intake of vegetables <2.5 kg/week, dietary intake of roughage <0.5 kg/week, smoking, high length of secondhand smoke exposure, history of fatty liver, history of diabetes, and first-degree history of liver cancer were the risk factors of liver cirrhosis in at-risk alcohol drinkers without HBV/HCV infection. Using these variables, we developed and validated a simple and noninvasive cirrhosis risk model. The model has good performance and could be used as a tool for triaging high-risk participants to prevent liver cirrhosis. Further prospective studies are required to validate the model in external populations.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

Y. Liu: Conceptualization, writing–original draft. **L.-W. Guo:** Validation, writing–review and editing. **H.-F. Xu:** Validation, writing–review and editing. **R.-H. Kang:** Data curation, writing–review and editing. **L.-Y. Zheng:** Data curation, writing–review and editing. **L.-Y. Zhang:** Data curation, writing–review and editing. **Q. Chen:** Data curation, writing–review and editing. **X.-B. Sun:** Data curation, writing–review and editing. **Y.-L. Qiao:** Conceptualization, writing–review and editing. **S.-K. Zhang:** Conceptualization, supervision.

Acknowledgments

This work was funded by Science and Technology Department of Henan Province (RKX202102011, to Y Liu).

The publication costs of this article were defrayed in part by the payment of publication fees. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

Note

Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

Received May 14, 2022; revised June 15, 2022; accepted July 20, 2022; published first July 27, 2022.

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