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Selection of high-risk individuals for esophageal cancer screening: A prediction model of esophageal squamous cell carcinoma based on a multicenter screening cohort in rural China

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Abstract

The mortality benefit of esophageal squamous cell carcinoma (ESCC) screening has been reported in several studies; however, the results of ESCC screening programs in China are suboptimal. Our study aimed to develop an ESCC risk prediction model to identify high-risk individuals for population-based esophageal cancer screening. In total, 86 745 participants enrolled in a population-based esophageal cancer screening program in rural China between 2007 and 2012 were included in the present study and followed up until December 31, 2015. Models for identifying individuals at risk of ESCC within 3 years were created using logistic regressions. The area under the receiver operating curve (AUC) was determined to estimate the model's overall performance. A total of 298 individuals were diagnosed with ESCC within 3 years after baseline. The model of ESCC included the predictors of age, sex, family history of upper gastrointestinal cancer, smoking status, alarming symptoms of retrosternal pain, back pain or neck pain, consumption of salted food and fresh fruits and disease

Abbreviations: +LR, positive likelihood ratio; AUC, area under the receiver operating curve; BMI, body mass index; CI, confidence interval; ESCC, esophageal squamous cell carcinoma; −LR, negative likelihood ratio; NNS, number needed to screen; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; UGI, upper gastrointestinal.

Wanqing Chen and He Li contributed equally to this study.

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history of peptic ulcer or esophagitis (AUC of 0.81; 95% confidence interval: 0.78-0.83). Compared to the current prescreening strategy in our program, the cut-off value of 10 in the score-based model could result in 3.11% fewer individuals subjected to endoscopies and present higher sensitivity, slightly higher specificity and lower number needed to screen. This score-based risk prediction model of ESCC based on eight epidemiological risk factors could increase the efficiency of the esophageal cancer screening program in rural China.

KEYWORDS

China, endoscopic screening, esophageal squamous cell carcinoma, individualized assessment, risk prediction

1 | INTRODUCTION

Esophageal cancer poses a considerable threat to the health of the Chinese population. In 2018, approximately half of global new cases and deaths of esophageal cancer occurred in China, and the disease burden of esophageal cancer occurring in rural areas was heavier.[1,2] The predominant histological type in China is esophageal squamous cell carcinoma (ESCC),[1,3] which is characterized by a poor prognosis because of the late-stage at diagnosis.[4] However, the 5-year survival rate of patients detected at an early stage could reach 80% or greater.[5] Evidence from some observational studies conducted in high-risk regions highlights the mortality benefit of ESCC screening.[5-7] Several government-funded mass endoscopy screening programs for esophageal cancer have been implemented in China since 2005,[8] including the Early Diagnosis and Early Treatment (EDET) program in rural China, the Esophageal, Stomach, Liver Cancer Screening Program (ESLCSP) in the four provinces of Jiangsu, Anhui, Shandong and Henan in rural China and the Cancer Screening Program in Urban China (CanSPUC). Currently, endoscopy with suspicious samplings of esophageal biopsies for histological examination is the gold standard for ESCC screening to diagnose esophageal cancer and precancerous lesions in China.[9] However, the eligibility criteria for endoscopies (ie, high-risk individuals) have remained an important and difficult challenge in mass esophageal cancer screening in this country.

The selection of individuals at a higher risk of esophageal cancer based on individual risk prediction models could be a more efficient strategy for large-scale esophageal cancer screening.[10-12] To the best of our knowledge, prediction tools that could be implemented in mass ESCC screening programs are limited. The questionnaire-based risk assessment tool (ie, the initial screening strategy) in the ESLCSP was the first to be used in an organized esophageal cancer screening program in China to select high-risk individuals for further endoscopic examinations. Our previous analysis found that this tool could predict the risk of developing ESCC in the general population, however, it still needs to be improved in selecting more sound predictors and forms and enhancing efficiency through individual risk evaluations.

Therefore, we undertook a population-based multicenter cohort study based on the ESLCSP to develop a score-based risk prediction model based on factors widely available from epidemiology questionnaires to predict an individual's risk of developing ESCC within 3 years.

What's new?

Esophageal squamous cell carcinoma (ESCC) poses a particularly considerable threat to the Chinese population and is usually characterized by poor prognosis. Here, the authors developed a prediction model of ESCC with good discriminative ability based on eight potential epidemiological risk factors—age, sex, upper gastrointestinal cancer family history, smoking status, retrosternal, back, or neck pain, salted food consumption, fresh fruit consumption, and peptic ulcer or esophagitis disease history. The prediction model could be used as a low-cost pre-screening tool for mass ESCC screening in China by identifying a limited group of high-risk individuals who may be considered for endoscopic screening.

2 | MATERIALS AND METHODS

2.1 | Study population

The participants considered in this risk prediction model of ESCC were included in a prospective cohort of the esophageal cancer screening component of the ESLCSP, which is an ongoing regionally organized cancer screening program in rural areas in four provinces (Jiangsu, Anhui, Shandong and Henan) in China. Regarding the esophageal cancer screening component of the ESLCSP program, cluster sampling was used to select candidate screening sites where counties had a relatively higher incidence and mortality of esophageal cancer. All women and men aged 40 to 69 years who had no history of cancer (self-reported), and had not received an endoscopic examination during the last 3 years (self-reported) in the selected villages (the smallest

unit) of the participating counties were approached through personal contact and phone invitation by trained local medical staff. Figure S1 shows the overview of the screening procedure applied in the esophageal cancer screening component of the ESLCSP. Briefly, all eligible participants were interviewed by trained staff to complete a baseline questionnaire to gather information regarding their exposure to potential risk factors (see the following section for detail) after explaining the study and obtaining written informed consent. The target population for further endoscopic examination was assessed using an initial assessment strategy (Table S1).

The inclusion criteria for the participants in the present study were as follows: (a) participants who were enrolled in the esophageal cancer screening component of the ESLCSP from 2007 to 2012 from the counties of Jinhu in Jiangsu Province, Panji in Anhui Province, Tengzhou in Shandong Province and Xiping in Henan Province; (b) participants who had no history of cancer confirmed by cancer registry data; (c) participants who had available data from baseline questionnaire survey; and (d) participants who signed an informed consent form.

The exclusion criteria were as follows: (a) participants who were diagnosed with cancer before recruitment and (b) participants with incomplete information in Table 1.

2.2 | Data collection and selection of candidate predictors of ESCC

The baseline questionnaire included age at enrollment, sex, socioeconomic status, source of drinking water, cigarette smoking, consumption of alcohol, family history of cancer and cancer type, dietary habits, self-reported clinical alarming symptoms, medication history and digestive system related disease history, such as peptic ulcer and esophagitis. In addition, all participants underwent anthropometric measurements, including height, weight, pulse rate and blood pressure, at baseline.

In the present study, candidate variables predictive of ESCC were identified based on the current literature, meta-analyses, high-quality studies conducted in regions with a high prevalence of esophageal cancer, evidence from the latest Chinese expert consensus and experience in early esophageal cancer screening in China.[9,10,13-26] The 11 candidate variables were age (40-44, 45-49, 50-54, 55-59, 60-64 or 65-69 years old); sex; cigarette smoking (noncurrent smokers, smokers for <30 pack-years or smokers for ≥30 pack-years); alcohol over-consumption (<15 or ≥15 g ethanol per day); body mass index (BMI; <18.5, 18.5-23.9 or ≥24 kg/m^2); intake of fresh fruit, salted food and high-temperature food (high or low; according to the intake frequency); family history of upper gastrointestinal (UGI) cancer (yes or no); alarming symptoms of any retrosternal pain, back pain or neck pain (yes or no); and disease history of peptic ulcer or esophagitis (yes or no). These predictors are listed in Table 1, and a detailed description of each variable is provided in the Supporting Information Methods.

2.3 | Outcome assessment

In the ESLCSP, all cancer screening sites are covered by the national cancer registry system, which collects statistics regarding the incidence and mortality of cancer. In the present study, the baseline data of the participants were annually linked to the cancer registry database of the county-level Centers for Disease Control and Prevention, which provided cancer data through December 31, 2015. Newly diagnosed cancers were classified by site according to the International Classification of Diseases, version 10 (ICD-10), and by histology based on the International Classification of Disease for Oncology, version 3 (ICD-O-3). The outcomes included all primary ESCCs (ICD-10 C15 with ICD-O-3 M8050-M8078 or M8083-M8084) diagnosed within 3 years from baseline.

2.4 | Statistical analysis

2.4.1 | Coefficient-based prediction models of ESCC

We developed a simple model and a more extensive prediction model (called the full model in the following text) based on different panels of predictive variables. In the simple model, the four best-established risk factors of ESCC, that is, age, sex, cigarette smoking and alcohol overconsumption, were included in the multivariable logistic model without any selection procedure. In the full model, we used a two-step approach to determine the panel of predictors in the final models. In the first step, the selection of predictors was based on a backward selection approach using a multivariable logistic regression model, in which the associations lost statistical significance at a predefined nominal significance level of 0.05. In the second step, the predictors that were eliminated in the first step were re-entered into the multivariable model one-by-one to ensure that no omitted predictor statistically significantly improved the goodness of fit in a likelihood ratio test. The Akaike information criterion (AIC) and area under the receiver operating curve (AUC) were used to determine the final model structure and coding form of the variables with multiple measures. Then, the pairwise interactions between the predictors were exhaustively tested in multivariate models, and no statistically significant interactions were found.

2.4.2 | Test of performance

The discriminative ability of the models was assessed by the AUC and its 95% confidence interval (95% CI) to test the model's ability to discriminate ESCC patients from control participants and by Somers' D statistic to assess the strength and direction of the associations between the predicted probabilities and observed responses.[27] The goodness of fit was assessed by Hosmer-Lemeshow (H-L) tests and calibration curves. We recalculated the statistics of the model

performance using both the leave-one-out and 10-fold cross-validation strategies to correct measures of predictive performance overfitting from the original development dataset. Such cross-validation processes calculated the unbiased AUC and Somers' D with the predicted probability of each subject or randomly selected group (10% of all individuals) from a model that ignores this subject or group.[28]

TABLE 1 Baseline characteristics of 86 745 individuals in the study cohort

Variables	Individuals with no ESCC (n, %)	Cases with ESCC (n, %)	*P*-value	OR
Total	86 447 (100.00)	298 (100.00)		
Sex			<.0001	
Women	48 531 (56.14)	118 (39.60)		Reference
Men	37 916 (43.86)	180 (60.40)		1.95 (1.55-2.46)
Age (years)			<.0001	
40-44	17 425 (20.16)	7 (2.35)		Reference
45-49	17 065 (19.74)	14 (4.70)		2.04 (0.82-5.06)
50-54	13 461 (15.57)	28 (9.40)		5.18 (2.26-11.86)
55-59	17 153 (19.84)	80 (26.84)		11.61(5.36-25.14)
60-64	12 691 (14.68)	92 (30.87)		18.05 (8.37-38.93)
65-69	8652 (10.01)	77 (25.84)		22.15 (10.22-48.05)
Cigarette smoking			<.0001	
No	69 154 (80.00)	172 (57.72)		Reference
Yes, pack-years				
<30	12 039 (13.92)	62 (20.80)		2.07 (1.55-2.77)
≥30	5254 (6.08)	64 (21.48)		4.90 (3.67-6.53)
Alcohol consumption (g per day)			<.0001	
<15	74 470 (86.15)	217 (72.82)		Reference
≥15	11 977 (13.85)	81 (27.18)		2.32 (1.80-3.00)
BMI (kg/m^2)			.0474	
<18.5	1196 (1.38)	9 (3.02)		2.28 (1.16-4.46)
18.5-23.9	52 946 (61.25)	175 (58.72)		Reference
≥24	32 305 (37.37)	114 (38.26)		1.07 (0.84-1.35)
Fresh Fruit			<.0001	
High	47 595 (55.06)	115 (38.59)		Reference
Low	38 852 (44.94)	183 (61.41)		1.95 (1.54-2.46)
Salted food			<.0001	
Low	66 616 (77.06)	178 (59.73)		Reference
High	19 831 (22.94)	120 (40.27)		2.27 (1.80-2.86)
Food temperature			.0080	
Low	67 842 (78.48)	215 (72.15)		Reference
High	18 605 (21.52)	83 (27.85)		1.41 (1.09-1.81)
Family history of UGI cancer			<.0001	
No	77 230 (89.34)	220 (73.83)		Reference
Yes	9217 (10.66)	78 (26.17)		2.97 (2.29-3.85)
Alarming symptoms[a]			<.0001	
No	80 947 (93.64)	254 (85.23)		Reference
Yes	5500 (6.36)	44 (14.77)		2.55 (1.85-3.52)
Relative disease history[b]			<.0001	
No	75 997 (87.91)	238 (79.87)		Reference
Yes	10 450 (12.09)	60 (20.13)		1.83 (1.38-2.44)

Abbreviation: UGI, upper gastrointestinal.

[a]Alarming symptoms including any current symptoms of retrosternal pain, back pain or neck pain.

[b]Relative disease history including any disease history of peptic ulcer or esophagitis.

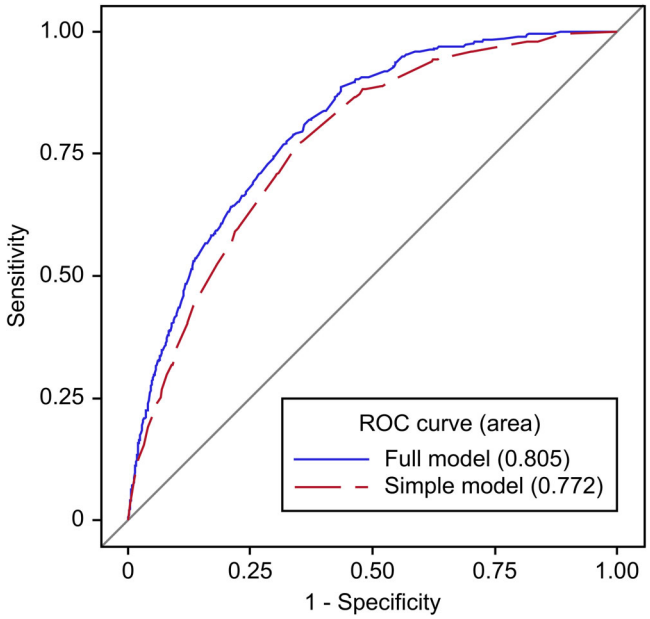

FIGURE 1 Receiver operating characteristic (ROC) curves based on the eight-variable full model (blue) and four-variable simple model (red). AUC, the area under the receiver operating characteristic curve [Color figure can be viewed at wileyonlinelibrary.com]

2.4.3 | Score-based model for stratifying the population for ESCC screening

The score-based model was created from the coefficient-based full model based on the study cohort. The risk scores of each predictor in the full model were calculated by dividing the minimum β-coefficient from the coefficient-based logistic model and rounding to the nearest 0.5.[11,29] The total risk score of each participant was calculated by summing the scores of each risk factor, and then, a score-based prediction model was developed. The tests of the performance of this score-based prediction model were the same as those applied to the coefficient-based model.

To provide recommendations for optimizing the current prescreening strategy in the esophageal cancer screening program of the ESLCSP, we comprehensively estimated some predominant indices for public health practices for each score cut-off value in the score-based model, including the number and proportion of high-risk individuals (ie, those recommended to undergo endoscopies), sensitivity, specificity, Youden's index (sensitivity + specificity − 1), accuracy rate, number needed to screen (NNS) to detect one ESCC case via endoscopy and predicted probability of developing ESCC within 3 years. The candidate cut-off values should have a higher sensitivity and a similar or lower proportion of high-risk individuals than those in the current prescreening strategy in the ESLCSP. Further, the effectiveness of these candidate cut-off values as new criteria for identifying high-risk individuals in the first 6 years of the ESLCSP (2007-2012) was compared to the current prescreening strategy in the ESLCSP through the indices mentioned above as well as the positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (−LR), odds ratio (OR, above vs below the score cut-offs) and AUC.

We performed several sensitivity analyses to assess the model's performance. First, we re-entered the three candidate predictors removed by the backward selection, that is, alcohol overconsumption, BMI and dietary habits of high-temperature food, into the multivariable model one-by-one by different categorized groups. Second, we re-assessed the AUC and AIC of two predictors included in the final model, that is, cigarette smoking and age, by altering the categorized groups. Third, we assessed the model's performance after adding additional predictors, which were not selected as candidate predictors of ESCC due to inefficient evidence, that is, fresh vegetables or moldy food. Fourth, we re-assessed the model's performance after excluding individuals who reported a history of alarming symptoms of dysphagia or odynophagia because these patients may already have ESCC.

The analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Study participants

In total, 91 131 women and men completed the questionnaire investigation in the esophageal cancer screening component of the ESLCSP between 2007 and 2012. After excluding 251 participants with any prior cancer diagnosis (ascertained by the cancer registry database) and 4135 participants with any missing variables in Table 1, 86 745 individuals were available for the final analysis as indicated in Figure S2. In total, 298 individuals were diagnosed with ESCC within 3 years after the baseline assessment. The median follow-up time was 4.66 years.

Table 1 reports the results of the univariate logistic regression analyses of the candidate predictive variables of ESCC in the study cohort. As shown in the table, the ESCC patients were more likely to be male, older, current smokers and alcohol over-consumers and have a lower BMI (<18.5), a family history of UGI cancer, alarming symptoms of retrosternal pain, back pain or neck pain, and a disease history of peptic ulcer or esophagitis. In addition, individuals with a higher consumption of salted food, higher intake of high-temperature food and lower consumption of fresh fruits were more likely to be at a higher risk of developing ESCC (Table 1).

3.2 | ESCC risk-prediction model: coefficient-based model

The simple prediction model included four variables, that is, age, sex, smoking and alcohol overconsumption. The ORs of these factors in the simple model are shown in Table 1. The full model predicting ESCC development within 3 years included the following eight variables: age, sex, family history of UGI cancer, cigarette smoking, dietary habits of consuming salted food or fresh fruits, alarming symptoms of

retrosternal pain, back pain or neck pain, and disease history of peptic ulcer or esophagitis (Table 2). No improvement in the AUC was apparent when other predictors were added or the final model was adjusted for the predictors (Table S2).

The receiver operating characteristic curves of the two prediction models without cross-validation are shown in Figure 1. Table 3 shows the discriminative ability of the two models without and with cross-validation. The AUC statistics without cross-validation were 0.805 (95% CI: 0.783-0.826) for the full model and 0.772 (95% CI: 0.748-0.796) for the simple model. The cross-validation provided slightly lower AUC statistics, that is, 0.795 (95% CI: 0.773-0.818) and 0.747 (95% CI: 0.722-0.773), after the leave-one-out cross-validation for the full and simple models, respectively, indicating minimal over-fitting and good discrimination. The performance of the two models was statistically good based on the goodness-of-fit tests (Table S3) and calibration curves (Figures S3 and S4). The AUCs were similar in the subcohort that excluded individuals with self-reported symptoms of dysphagia or odynophagia (Table S4).

3.3 | ESCC risk-prediction model: score-based model

The score-based model assigned an additional score based on the coefficient-based full model. Table 2 reports the risk scores for each predictor, which constituted the score-based model for ESCC as follows: age (2.5 for 45-49 years old; 5.0 for 50-54 years old; 7.5 for 55-59 years old; 9.0 for 60-64 years old; 9.5 for 65-69 years old), sex (1.5 for men), family history of UGI cancer (2.5 for yes), smoking status

TABLE 2 Risk factors associated with esophageal squamous cell carcinoma in the multivariable logistic model and the assigned scores

Variables	Regression coefficient	Adjusted OR (95% CI)	Assigned Scores
Age (years)			
40-44		1.00 (reference)	0
45-49	0.687	1.99 (0.80-4.93)	2.5
50-54	1.483	4.41 (1.92-10.11)	5.0
55-59	2.242	9.41 (4.34-20.44)	7.5
60-64	2.664	14.35 (6.63-31.07)	9.0
65-69	2.830	16.94 (7.78-36.89)	9.5
Sex			
Women		1.00 (reference)	0
Men	0.377	1.46 (1.10-1.93)	1.5
Family history of UGI cancer			
No		1.00 (reference)	0
Yes	0.777	2.17 (1.65-2.86)	2.5
Cigarette smoking			
No		1.00 (reference)	0
Yes, pack-years			
<30	0.455	1.58 (1.14-2.18)	1.5
≥30	0.733	2.08 (1.48-2.92)	2.5
Salted food			
Low		1.00 (reference)	0
High	0.502	1.65 (1.30-2.10)	1.5
Fresh fruits			
High		1.00 (reference)	0
Low	0.289	1.34 (1.05-1.70)	1.0
Alarming symptoms[a]			
No		1.00 (reference)	0
Yes	0.591	1.81 (1.29-2.53)	2.0
Relative disease history[b]			
No		1.00 (reference)	0
Yes	0.417	1.52 (1.13-2.03)	1.5

Abbreviation: UGI, upper gastrointestinal.

[a]Alarming symptoms including any current symptoms of retrosternal pain, back pain or neck pain.

[b]Relative disease history including any disease history of peptic ulcer or esophagitis.

TABLE 3 Statistics of the performance of developed logistic risk-prediction models of ESCC

	Original without cross-validation		10-fold cross-validation		Leave-one-out cross-validation	
Model	AUC (95%CI)	Somers' D	AUC (95%CI)	Somers' D	AUC (95%CI)	Somers' D
Full model	0.805 (0.783-0.826)	0.610	0.798 (0.776-0.819)	0.595	0.795 (0.773-0.818)	0.590
Simple model	0.772 (0.748-0.796)	0.544	0.758 (0.733-0.783)	0.516	0.747 (0.722-0.773)	0.495

TABLE 4 Performance of a risk scoring prediction model of esophageal squamous cell carcinoma with different score cut-offs in the study cohort

Score cut-off	High-risk individuals (n, %)	True ESCC (n)	Sensitivity (%)	Specificity (%)	Youden's index	Accuracy rate (%)	NNS	Probability (%)
1	82 978 (95.66)	298	100.00	4.36	0.04	4.69	278	0.02
2	76 891 (88.64)	298	100.00	11.40	0.11	11.70	258	0.03
3	70 831 (81.65)	296	99.33	18.41	0.18	18.68	239	0.04
4	66 439 (76.59)	294	98.66	23.48	0.22	23.74	226	0.06
5	61 091 (70.43)	291	97.65	29.67	0.27	29.90	210	0.08
6	54 202 (62.48)	287	96.31	37.63	0.34	37.83	189	0.11
7	48 082 (55.43)	280	93.96	44.70	0.39	44.87	172	0.15
8	42 041 (48.47)	270	90.60	51.68	0.42	51.81	156	0.20
9	37 584 (43.33)	261	87.58	56.83	0.44	56.93	144	0.27
10	29 586 (34.11)	236	79.19	66.05	0.45	66.09	125	0.36
11	19 727 (22.74)	194	65.10	77.40	0.43	77.36	102	0.48
12	13 975 (16.11)	168	56.38	84.03	0.40	83.93	83	0.64
13	8885 (10.24)	127	42.62	89.87	0.32	89.71	70	0.87
14	5419 (6.25)	97	32.55	93.84	0.26	93.63	56	1.16
15	2809 (3.24)	59	19.80	96.82	0.17	96.55	48	1.56
16	1490 (1.72)	34	11.41	98.32	0.10	98.02	44	2.09
17	644 (0.74)	19	6.38	99.28	0.06	98.96	34	2.79
18	305 (0.35)	8	2.68	99.66	0.02	99.32	38	3.73
19	98 (0.11)	1	0.34	99.89	0.00	99.55	98	4.95
20	44 (0.05)	1	0.34	99.95	0.00	99.61	44	6.56

Note: There were no ESCC cases in the score of 21 or 22; therefore, we do not display the corresponding statistics of these two cut-off values.
Abbreviations: ESCC, esophageal squamous cell carcinoma; NNS, number needed to screen to detect one case of ESCC.

(1.5 for yes and smoking <30 pack-years and 2.5 for yes and smoking ≥30 pack-years), higher consumption of salted food (1.5 for yes), lower consumption of fresh fruits (1.0 for yes), alarming symptoms of retrosternal pain, back pain or neck pain (2.0 for yes) and disease history of peptic ulcer or esophagitis (1.5 for yes); the total risk scores of each individual ranged from 0 to 22. The AUC of the score-based model was 0.804 (95% CI: 0.783-0.826; Table S5), which is similar to that of the coefficient-based full model. In addition, the model had good calibration based on the goodness-of-fit tests (χ^2 = 4.984, P = .759 in the H-L test; Table S3) and calibration curves (Figure S5). A slightly lower discriminatory ability was observed in the internal validation cohort, with AUCs in the 10-fold cross-validation of 0.802 (95% CI: 0.780-0.824; Table S5) and leave-one-out cross-validation of 0.789 (95% CI: 0.767-0.812; Table S5).

3.4 | Effectiveness of the score-based prediction model of ESCC

Table 4 shows the discriminative performances of each score as a cut-off value in identifying individuals at a high risk of ESCC in the general population. As the cut-off value increased, the risk of ESCC increased, and the proportion recommended to undergo endoscopies and the sensitivity in detecting ESCC cases decreased. Given that the sensitivity for ESCC and the proportion of high-risk individuals in the current ESLCSP were 64.43% and 35.20%, respectively, the candidate cut-off values of 10 and 11 from the score-based model were selected as the new criteria for identifying high-risk individuals for endoscopies to optimize the current prescreening strategy (Table 5).

TABLE 5 Comparing the current prescreening strategy in the ESLCSP with the score-based risk prediction model

Performance index	Current prescreening strategy in the ESLCSP	Recommended new eligibility criteria for endoscopies	
		Cut-off value of 10 in the score-based model	Cut-off value of 11 in the score-based model
High-risk individuals (n, %)	30 536 (35.20)	29 586 (34.11)	19 727 (22.74)
True ESCC cases (n)	192	236	194
Sensitivity (%)	64.43	79.19	65.10
Specificity (%)	64.90	66.05	77.40
Youden's index	0.29	0.45	0.43
Accuracy rate (%)	64.90	66.09	77.36
PPV (%)	0.63	0.80	0.98
NPV (%)	99.81	99.89	99.84
+LR	1.84	2.33	2.88
−LR	0.55	0.32	0.45
NSS	159	125	102
OR (95% CI)	3.35 (2.64-4.25)	7.41 (5.60-9.80)	6.39 (5.03-8.11)
AUC (95% CI)	0.65 (0.62-0.67)	0.73 (0.70-0.75)	0.71 (0.69-0.74)

Abbreviations: +LR, positive likelihood ratio; AUC, area under the receiver operating characteristics curve; ESCC, esophageal squamous cell carcinoma; −LR, negative likelihood ratio; NNS, number needed to screen to detect one case of ESCC; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

Compared to the prescreening strategy in the ESLCSP, if the new criteria using the cut-off value of 10 were applied to select individuals for endoscopies during the 2007-2012 period of the ESLCSP, 3.11% (29 586 vs 30 536) fewer individuals would be selected and 22.92% (236 vs 192) more ESCC cases would be detected (Table S6). Regarding the identification of ESCC cases, the cut-off value of 10 in the score-based model had a higher sensitivity (79.19% vs 64.43%), a slightly higher specificity (66.05% vs 64.90%) and a lower NNS (125 vs 159) than the current prescreening strategy in the ESLCSP (Table 5), that is, the efficiency of screening in the ESLCSP can be improved by applying this new criterion to the identification of high-risk populations needing endoscopies. In addition, the results showed that if this new cut-off had been applied in the ESLCSP during the 2007 to 2012 period, a higher proportion of men and participants aged in their 60s would have been recommended to undergo endoscopies (Table S7).

When the cut-off value of 11 in the score-based model was applied to the identification of individuals for endoscopies, the obtained effectiveness was higher than that of the current prescreening strategy, and 10 809 (12.46%) endoscopies could have been avoided given the slightly higher sensitivity (65.10%) in detecting ESCC cases (Table 5).

4 | DISCUSSION

In the present study, we developed a score-based individual risk prediction model of ESCC based on data routinely collected in epidemiological questionnaires to provide a simple and efficient tool for the selection of high-risk individuals for mass esophageal cancer screening in the Chinese population. This model included the variables age, sex, family history of UGI cancer, smoking status, alarming symptoms of retrosternal pain, back pain or neck pain, consumption of salted food, consumption of fresh fruits and disease history of peptic ulcer or esophagitis and showed good discriminative ability with an AUC of 0.805 (95% CI: 0.783-0.826). After the internal validation, the performance of this model slightly decreased to 0.795 (95% CI: 0.773-0.818) in the leave-one-out cross-validation. For practical use, we developed a score chart (Table 2) for each predictor to easily and visually evaluate the risk of ESCC for each participant. More importantly, this model provides more accurate and quantitative strategies to optimize the current prescreening strategy in the ESLCSP.

To the best of our knowledge, only three previous prediction models of ESCC were developed based on lifestyle-related data from population-based case-control studies in China, Sweden and Iran.[10,15,16] The factors in these models included five predictors similar to those in our score-based risk prediction model of ESCC (ie, age, sex, cigarette smoking, consumption of fresh fruits and family history of UGI cancer) and other predictive variables. These earlier models showed good discriminative performance, with AUC statistics ranging from 0.77 to 0.81; however, the ESCC model based on the Iran population had a poor calibration ability, with $P < .01$ in the H-L test.[10,15,16] This study provides the first prediction model of ESCC based on a population-based cohort study with good discrimination, that is, an AUC of 0.805 (95% CI: 0.783-0.826), and good calibration. The score-based model developed based on the coefficient-based prediction model of ESCC also showed good performance metrics, with an AUC of 0.804 (95% CI: 0.783-0.826). We also calculated and compared the AUCs of the coefficient-based full model with other three models (the nongenetic model of ESCC developed in a Chinese population,[18]

the simple model of ESCC developed in a Sweden population,[15] and the prescreening method used in the ESLCSP; Table S8) in our study cohort and collected relative predictors included in these models or eligibility criteria. Our analysis showed that the full model developed in our study had a more significant discrimination ability ($P < .0001$), which was compared using the PROC Logistic function in SAS.

In the present study, many well-known environmental risk factors of ESCC were included in the final model, including the five major risk factors mentioned above and three other potential factors of ESCC based on a high-quality literature review, meta-analyses and the latest Chinese expert consensus and experience in early esophageal cancer screening in China, that is, the consumption of salted food, nonspecific alarming symptoms of retrosternal pain, back pain or neck pain, and disease history of peptic or duodenal ulcers or esophagitis.[9,10,13-26] The other potential risk factors of ESCC, that is, heavy consumption of alcohol, BMI and consumption of high-temperature food, excluded from the multivariable backward logistic analysis and the predictor of consumption of moldy food, included in the prescreening strategy in the ESLCSP, did not improve the model's overall performance in this analysis, regardless of how their categorized classification values changed (Table S2). These findings might suggest that the associations between these factors and the risk of ESCC might be weaker than the association with other robust risk factors, such as age and family history of UGI cancer, in our study population. In the present study, we did not include the predictors of dysphagia or odynophagia in the prediction model of ESCC because patients with these specific symptoms might already have ESCC, which would diminish the benefit of early detection using the prediction model. However, it should be noted that those individuals with self-reported alarming symptoms of dysphagia or odynophagia had a higher risk for developing ESCC in our whole study population (adjusted OR = 1.70, 95% CI: 1.18-2.51).

As far as we know, two previous ESCC prediction models were developed based on the Chinese population.[10,18] Compared to them, our model might have some merits. First, from the aspect of the study design and data resources used in the model development, the previous two models were developed based on data from a multicenter hospital-based case-control study[18] and a single-center population-based case-control study in an area with a high prevalence of ESCC in China.[10]Our study was the first multicenter population-based cohort study to develop a prediction model of ESCC in the Chinese population, thus rendering the model more representative. In addition, each participant in our cohort had a follow-up time of at least 3 years, which resulted in more ESCC cases for model development. Second, from the aspect of selection of predictors, we noticed that some predictors included in the model developed by Liu et al,[10] such as coal or wood used as the main source of cooking fuel, pesticide exposure and irregular eating habits, are not well-known major risk factors for ESCC, for example, cigarette smoking. To the best of our knowledge, these variables were not collected in three ongoing organized ESCC screening programs in China, including the ESLCSP. Therefore, we cannot estimate the model accuracy and practice value as a prescreening method in the ESLCSP given the limitation of the same predictors. Compared to this model, two steps were used to select the predictors for the final ESCC model in the present study, that is, practical and statistical aspects, which were described in detail in the methods section. We believe that more comprehensive estimates could improve the model's ability to identify more potential cases of ESCC. In addition, the ESCC model developed by Chang et al included 25 single nucleotide polymorphisms (SNPs) and four nongenetic factors (sex, age, smoking and drinking), which improved the model's accuracy but limited its applicability as an easy-to-use and low-cost assessment tool in a population-based ESCC screening program.

Compared to previous models of ESCC, the primary benefit of our model could be that it provides directly feasible recommendations or strategies for optimizing the current prescreening method in an ongoing ESCC screening program in China without incurring any extra costs. The two key strategies must be considered when identifying cut-off values from the score-based model as the recommended new criteria for identifying high-risk individuals who should undergo endoscopies in the ESLCSP. The first strategy is to choose cut-off values that identified the same (lower is best) high-risk individuals as the current prescreening method in the ESLCSP but had a higher sensitivity and specificity and a lower NNS, which could improve the efficiency of screening without increasing the cost. Accordingly, the cut-off value of 10 in the score-based model meets this requirement, that is, a 14.76% absolute increase in sensitivity in ESCC prediction within 3 years, a 1.15% absolute increase in specificity, an absolute decrease of 34 in terms of the NNS in detecting one ESCC case, and a slightly lower proportion of the high-risk population compared to the current prescreening strategy in the ESLCSP (Table 5). This finding indicated that a greater screening efficiency could be obtained if this cut-off had been applied between 2007 and 2012 in the ESLCSP. The second strategy is to choose a cut-off value that had a sensitivity (higher is best) similar to the current prescreening method in the ESLCSP but could decrease the proportion of high-risk individuals, which may help save costs associated with endoscopic examination without decreasing the screening efficiency. Accordingly, the cut-off value of 11 in the score-based model meets this requirement. This value had a slightly higher sensitivity in identifying ESCC (65.10%) than the current method in the ESLCSP (64.43%) and can decrease the number of endoscopies by 12.46% (ie, 10 809 endoscopies between 2007 and 2012 in the ESLCSP), indicating that approximately 3.78 million RMB (calculated as 350 RMB per endoscopic examination) could have been saved.

Based on these considerations, we believe that the cut-off values of 10 or 11 in the score-based model can optimize the current screening strategy in the ESLCSP. Because the ESLCSP is a National Key Public Health Project, it is more suitable to choose a new strategy for identifying cases more accurately without increasing extra cost rather than a strategy of decreasing costs but losing more patients. Therefore, we recommend the cut-off value of 10 in the score-based model as the new eligibility criterion for identifying the target population for endoscopies in the ESLCSP. Additionally, we compared the

distribution of the stratification of the participants and the proportion of high-risk individuals by age and sex based on the cut-off value of 10 in the score-based model and current prescreening strategy (Tables S6 and S7). This analysis showed that if this new cut-off value had been applied in the ESLCSP from 2007 to 2012, an additional 11.12% of men would have been recommended to undergo endoscopies compared to the current prescreening strategy (Table S7). This approach could be more suitable and obtain a higher efficiency because men had a higher risk of developing esophageal cancer than women in China. Notably, if the ESLCSP adopted this new eligibility criterion, then the proportion of participants in different age-groups recommended to undergo endoscopies would have greatly changed. Specifically, it would have increased the recommendation for additional endoscopies for 47.19% of the participants aged in their 60s and decreased such recommendations for 30.5% of the participants aged in their 40s. Although we believe that the recommendation for endoscopies in older participants is reasonable because these individuals have a higher incidence risk of esophageal cancer than younger individuals, we suggest that the ESLCSP needs more detailed analyses and debates on the suitability of the proportion of different age-groups recommended for endoscopies. In addition, if other population-based ESCC screening programs seek to adopt this score-based model as a prescreening tool before endoscopic examinations, we must note that the selection of cut-off values should be carefully considered based on practical criteria, including the population-based disease burden of esophageal cancer, available funding and so on.

4.1 | Strengths

The main strength of our study is that it was the first multicenter population-based cohort study to develop a prediction model of ESCC in the Chinese population, thereby rendering the model more representative. Furthermore, detailed epidemiological questionnaire information was collected in a standardized manner by trained study staff to ensure the quality of the data. A sound annual passive follow-up mechanism for the entire cohort population was established and carried out in our program based on the cancer registration system; therefore, we could obtain information regarding each participant's cancer incidence in the cohort. In addition, we created a risk scoring system that provided an easy tool for public health practitioners to facilitate the calculation of the individual risk of developing esophageal cancer within 3 years since questionnaire survey, which provided direct feasible recommendations or strategies for optimizing the current prescreening method in an on-going ESCC screening program in China without incurring any extra costs.

4.2 | Limitations

There are also several potential limitations in the present study. First, although the study population was large and recruited from general communities in four counties in four provinces in China, the sample still cannot represent all rural populations aged 40 to 69 years in China. Therefore, selection bias cannot be ruled out. Second, this model needs to be validated in other Chinese populations to evaluate whether it can be implemented in screening practice. External validations will be conducted based on a randomized controlled trial of endoscopic screening for UGI cancer when data are available to solve this issue. Third, we cannot exclude existing recall bias and self-reported bias from the baseline survey, although this survey was conducted in a standardized manner by trained staff; additionally, we also cannot exclude leading time bias due to endoscopic screening. Fourth, we must note that although the population enrolled in the study cohort was large, the actual number of ESCC patients was small, which may have caused issues with residual bias. We believe that this issue could be solved by further follow-up. Fifth, we did not conduct health economic evaluations to compare the cost-effectiveness of different initial screening strategies; thus, the results might not be adequately robust when we refer to our model as more cost-effective than the current initial screening strategy in the ESLCSP. We will perform further investigations to confirm the effectiveness of this new approach by implementing a community-based cost-effectiveness analysis.

5 | CONCLUSIONS

In summary, we developed a score-based risk prediction model of ESCC based on eight epidemiological factors that could facilitate the selection of high-risk individuals for population-based esophageal cancer screening in the Chinese population. This model can optimize the current prescreening strategy in the ESLCSP. A further cost-effective study should be conducted to test its actual effectiveness and feasibility.

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CONFLICT OF INTEREST

The authors have no conflicts of interest or financial interests to disclose.

ETHICS STATEMENT

Each participant involved in this program signed informed consent. The research protocols for the ESLCSP were independently approved by the Institutional Review Board of the Cancer Institute/Hospital, Chinese Academy of Medical Sciences (CICAMS, NCC1788).

DATA AVAILABILITY STATEMENT

Additional summary tables, sensitivity analyses and data used in this research are available upon reasonable request from the corresponding authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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