Update and validation of a diagnostic model to identify prevalent malignant lesions in esophagus in general population

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Summary

Background Previous risk prediction models taking esophageal malignant lesions detected during endoscopy as the primary outcome are not always sufficient to identify prevalent cases which are "overlooked" at screening. We aimed to update and externally validate our previous risk prediction model for malignant esophageal lesions by redefining the predicted outcome.

Methods 15,192 individuals from the Endoscopic Screening for Esophageal Cancer in China randomized controlled trial (ESECC trial, NCT01688908) were included as the training set, and 4576 participants from another population-based esophageal squamous cell carcinoma (ESCC) screening cohort (Anyang Esophageal Cancer Cohort Study, AECCS) served as the external validation set. Lesions with severe dysplasia or worse diagnosed at chromoendoscopy or identified via follow-up within 1 year after screening were defined as main outcome. Logistic regressions were applied to reconstruct the questionnaire-based prediction model using information collected before screening, with Akaike Information Criterion to determine the model structure.

Findings The final prediction model included age and its quadratic term, family history of ESCC, low body mass index ($\leq$22 kg/m^2), use of coal or wood as main fuel for cooking, eating rapidly, and ingestion of leftover food. The area under the curve was 0·77 (95% CI: 0·73–0·80) and 0·71 (95% CI: 0·65–0·78) in the training and validation set. When screening the top 50% or 10% of high-risk individuals within population, the detection rates can be increased in both cohorts, as compared to universal screening.

Interpretation The described tool may promote the efficiency of current national screening programs for ESCC and contribute to a precision screening strategy in high-risk regions in China.

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Research in context

Evidence before this study

We searched PubMed to identify articles published until June 2021 using the key search words ("risk prediction" OR "risk score") AND ("esophageal cancer", "ESCC"), and found that published prediction models for esophageal squamous cell carcinoma (ESCC) mainly took clinically diagnosed cancer patients identified via follow-up as outcome, which cannot precisely discriminate prevalent cases at screening phase from the general population. We previously developed a model taking esophageal malignant lesions detected during endoscopy as primary outcome and this study aimed to update and externally validate our previous questionnaire-based risk prediction model by redefining the outcome as esophageal malignant lesions detected at baseline screening and ESCC cases diagnosed within 1 year after screening.

Added value of this study

The updated prediction model showed good discrimination and was validated in an external population. Detection rates of malignances could be increased by 70% if our model is integrated into the current esophageal cancer screening program in China.

Implications of all the available evidence

The new version of our diagnostic model might be useful as precision screening tool for esophageal cancer in the general population, and the future application of our model may bring changes to the traditional screening strategy.

Introduction

Esophageal cancer is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer-related death worldwide.[1] Over half of the newly diagnosed cases of esophageal cancer occur in China yearly,[1,2] where esophageal squamous cell carcinoma (ESCC) is the main histologic subtype.[3] Early detection and treatment can reduce ESCC mortality by 30–60%,[4,5] and population-level screening is a critical element for ESCC prevention.

Population-level ESCC screening programs using Lugol's chromoendoscopy have been widely implemented in high-risk regions in China,[5–7] and almost all of which have adopted a universal screening strategy.[8] Under this strategy, over 2 million endoscopies have been performed while the detection rate was only 0.9%, less than 2.9% even in regions with extremely high incidence.[6,8,9] Since screening for ESCC is resource-intensive and has the potential for harm due to the invasive nature of endoscopic examination and biopsy, a precision screening strategy is needed for exclusion of low-risk subgroups from initial screening.[10] The questionnaire-based risk assessment has been accepted as a promising risk enrichment approach to accurately and conveniently identify subjects at high risk for ESCC prior to large-scale endoscopic screening.[10]

In 2017, we constructed a questionnaire-based prediction model to identify high-risk individuals using baseline data from the Endoscopic Screening for Esophageal Cancer in China (ESECC) randomized controlled trial.[11] This offers a population-based risk stratification tool for massive ESCC screening modalities in high-risk regions in China. In this previous study, severe dysplasia and above (SDA, including severe dysplasia, carcinoma *in situ*, and ESCC) where lesions which were detected with endoscopic screening were defined as outcome events, and prediction models were developed separately in subgroups of subjects aged 45–60 years and 61–69 years to model the varying effect of the age variable. As progress has been made over the past few years, a growing body of evidence has shown that defining outcome events based solely on the yield under endoscopy is insufficient to identify a handful of prevalent cases that are "overlooked" at screening.[12,13] On the other hand, although our age-stratified model-building strategy increased the accuracy of fit in subgroups, it introduced the inconvenience of interpreting the gap of predicted risk for subjects at the age boundary between subgroups.

In this study, we updated our previous risk prediction model for ESCC by making the following changes: First, we re-defined the outcome events by incorporating SDA detected at baseline screening and ESCC cases diagnosed within 1 year after screening. Second, we added nonlinear terms for the age variable and fitted a whole age model (45–69 years), instead of fitting separate models in different age subgroups. Finally, we externally validated the updated version of our risk prediction model in another ESCC screening cohort in a neighboring region that is high-risk for ESCC, to evaluate the generalizability and real-world performance of

our risk stratification tool when applied in population-level ESCC screening programs.

Methods

Study population

Training cohort. Participants in the training cohort were enrolled from the screening arm of the ESECC trial.[7] The ESECC trial was initiated in 2012 in Hua County, Anyang, Henan Province, which is a high-risk region for ESCC in China. A total of 668 villages in Hua County were randomly selected and assigned to the screening arm or the control arm at a ratio of 1:1 by means of blocked randomization based on population size.[7] In the screening arm, 15,299 participants (inclusion criteria listed in supplementary materials) completed chromoendoscopy and the questionnaire investigation following standard procedures and strict quality control.[7] After excluding 7 ESCCs before recruitment and 100 subjects without available data regarding body mass index (BMI), 15,192 subjects were eligible for use in development of the risk prediction model.

Validation cohort. Participants for validation were enrolled from another population-based ESCC screening cohort, Anyang Esophageal Cancer Cohort Study (AECCS)[4,14] conducted in 10 villages from 4 counties in the Taihang mountain area. All eligible participants (inclusion criteria listed in supplementary materials) in target villages were invited by village committees, and 9375 subjects (> 80% coverage of the target population) were finally enrolled. There were three cross-sections of endoscopic screening, which occurred in 2006–2007, 2007–2009 and 2013–2016. In each cross-section, all cohort members were invited to have chromoendoscopy and a questionnaire investigation, and 9315 subjects with at least one valid endoscopic examination were included in the current study. To exhaustively identify SDA cases among AECCS cohort members, we used information regarding their last endoscopic examination and the respective questionnaire investigation. The AECCS shared a screening and questionnaire protocol identical to that in the ESECC trial. To keep the age range in complete agreement with that in the training cohort, 4576 subjects aged 45–69 years at their last endoscopy were included.

Data collection

Predictors. Participants enrolled in both the training and validation cohort received a physical examination and a computer-aided one-on-one questionnaire investigation to collect potential predictors including demographic factors, lifestyle information, ESCC related symptoms, and ESCC family history.[7,14] Variables collected in these two cohorts can be found in the Supplementary materials.

Predicted outcomes. The predicted outcome was defined as SDA detected at baseline screening and interval cancer diagnosed within 1 year after screening. For both cohorts, standard upper gastrointestinal (UGI) endoscopy with Lugol's iodine staining was carried out to examine the esophagus by experienced physicians. Biopsies were taken if abnormal epithelium was observed under white light or after iodine staining. For subjects without visually identifiable lesions, standard biopsies were taken at the mid-esophagus (28 and 33 cm from the incisors in the 6 o'clock position). Biopsies were fixed in 10% formaldehyde, embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin (H&E). Pathologic diagnosis of biopsy specimens was performed by two experienced pathologists blinded to endoscopic findings, and discrepancies in pathologic diagnoses were adjudicated by consultation. Pathologic diagnosis of biopsied lesions included normal mucosa, acanthosis, esophagitis, basal cell hyperplasia, mild dysplasia, moderate dysplasia, severe dysplasia, carcinoma *in situ* and squamous cell carcinoma. The pathologic diagnosis of highest degree of severity among the biopsies for each subject was regarded as the final diagnosis.

To identify incident ESCC cases together with death events from any cause after screening, we implemented active annual door-to-door interviews and passive linkage with local electronic registry data in both the ESECC trial and the AECCS.[15–17] Active door-to-door follow-up was conducted by well-trained village doctors and community leaders of target villages. Passive follow-up was achieved by linkage with: (1) the New Rural Cooperative Medical Scheme (NCMS), wherein the government runs a medical insurance system with a coverage of nearly 100% in this area to identify incident cancer cases; and (2) the all-cause death surveillance system to identify death events.[15–17]

Statistical analysis

Model construction. Candidate questionnaire-based predictors assessed in the training cohort included age, gender, family history of ESCC, BMI, cigarette smoking, alcohol drinking, unhealthy dietary habits, ESCC related symptoms, use of coal or wood as a main cooking fuel in the household, exposure of fumes in the kitchen, and sources of drinking water and pesticide exposure. The definition and coding form for each candidate predictor can be found in the Supplementary materials. All candidate predictors were first evaluated using a univariate logistic regression model, and variables with odds ratio (OR) >1·3 and *P*-value<0·5 were subjected to a multivariate logistic regression model for

further selection. The structure of the final prediction model was determined by Akaike Information Criterion (AIC). A quadratic term for age was added in the model to fit the nonlinear effect of age in predicting the risk of ESCC. We also performed two sets of sensitivity analysis to evaluate the robustness of our model structure by: (1) setting a different time window (1 month, 3 months, 6 months, 1 year, 2 years, 3 years, or 5 years after screening) for defining interval cancers which should be included as outcome events; (2) fitting age by restricted cubic splines instead of quadratic term to model the nonlinear effects of the age variable.

Model performance in training and validation cohorts. The performance of the final prediction model in discriminating high-risk individuals for ESCC in both the training and validation cohorts is shown in the receiver operating characteristic (ROC) curve, and quantified using area under the curve (AUC). In the training cohort, we also performed leave-one-out cross-validation in which the model's probability of overfitting was evaluated based on the predicted probability of each subject generated from models built on all the remaining subjects. The calibration capability of our prediction model was visually evaluated with calibration plots and statistically tested with the Hosmer and Lemeshow Test. Recalibration was performed using the Platt Scaling method.

Application of model-based tailored screening. We assessed the application performance of our model by assuming a hypothetic model-based tailored screening. Subjects in the training and validation cohorts were divided into 10 risk categories by deciles based on their predicted probabilities. The detection rate ratio and number of subjects need to be screened for detecting one case were calculated under these decile-based proportions of coverage of endoscopic screening by setting universal screening as the reference.

All statistical analysis was conducted using STATA version 14.0 and R version 3.5.1. *P* values were two sided and had a significance level of 0·05.

Ethical considerations

This study was approved by the Institutional Review Board of the Peking University School of Oncology, China, and written informed consent was obtained from each participant in this study.

Role of funding sources

This work was supported by the National Natural Science Foundation of China (82073626, 81773501), the National Science & Technology Fundamental Resources Investigation Program of China (2019FY101102), the National Key R&D Program of China (2021YFC2500405), the Beijing-Tianjin-Hebei Basic Research Cooperation Project (J200016), the Digestive Medical Coordinated Development Center of Beijing Hospitals Authority (XXZ0204) and the Beijing Nova Program (Z201100006820093). Sponsors had no role in the study design, data collection, analysis, and interpretation of data. Furthermore, all authors had full access to all the preliminary data in the study and accept responsibility to submit for publication.

Results

Description of the training and validation cohorts

A total of 15,192 subjects in the screening arm of the ESECC trial and 4576 subjects from the AECCS were analyzed for this study as training and validation datasets. At endoscopic screening, 113 cases of SDA (0·74%) and 52 cases of SDA (1·14%) were detected, and an additional 10 and 4 subjects were diagnosed with ESCC within 1 year after screening in the training and validation cohorts. The training and validation cohorts showed significant differences in the majority of demographic characteristics and lifestyle variables. Compared to the training set, individuals in the validation set were younger, and there were more females, more subjects with low BMI (≤22 kg/m^2), more subjects reporting use of coal or wood as a main cooking fuel, and more individuals ingesting leftover food (≥ 1 time per week). However, fewer subjects in the validation set preferred high temperature food, and fewer subjects preferred to eat rapidly (Table 1).

Model structure and its performance

The final model included seven predictors consisting of age, a quadratic term of age, family history of ESCC, low BMI (≤22 kg/m^2), use of coal or wood as a main cooking fuel, eating rapidly, and ingestion of leftover food (≥ 1 time per week) (Table 2). In the training cohort, the AUC of the model was 0·77 (95% Confidence Interval (CI): 0·73–0·80) (Figure 1), and leave-one-out cross-validation generated a slightly lower AUC of 0·75 (95% CI: 0·72–0·79) (Figure 1). When applied to the validation cohort, the prediction model still showed ideal performance, with an AUC of 0·71 (95% CI: 0·65–0·78) (Figure 1). As shown in Supplementary Figure 1, the model showed good calibration in the training cohort (*P*-value for Hosmer-Lemeshow Test = 0·43) and in the validation cohort after recalibration (*P*-value for Hosmer-Lemeshow Test = 0·30).

Application of model-based tailored screening

The performance of our model was assessed under three most likely application scenarios. When the top 80% of high-risk individuals accepted endoscopies, very high sensitivities (99·19% and 94·64%) could be achieved in the training and validation cohorts (Table 3). When one chose a probability cutoff to screen 50% of

Variables	Training Set, n (%)	Validation Set, n (%)	*P*-values
Age (y)			
Median (interquartile range)	58 (50, 63)	54 (49, 60)	<0·01*
Gender			
Female	7716 (50·79)	2468 (53·93)	<0·01*
Male	7476 (49·21)	2108 (46·07)	
Family history of ESCC [a]			
0	13,523 (89·01)	4069 (88·92)	0·06
1	1356 (8·93)	431 (9·42)	
2	244 (1·61)	67 (1·46)	
3–5	69 (0·45)	9 (0·20)	
BMI (kg/m^2)			
>22	12,462 (82·03)	3600 (78·67)	<0·01*
<=22	2730 (17·97)	976 (21·33)	
Smoking			
No	11,350 (74·71)	3435 (75·07)	0·63
Yes	3842 (25·29)	1141 (24·93)	
Use of coal or wood as main cooking fuel			
No	7505 (49·40)	849 (18·55)	<0·01*
Yes	7687 (50·60)	3727 (81·45)	
Pesticide exposure			
No	5762 (37·93)	1764 (38·55)	0·45
Yes	9430 (62·07)	2812 (61·45)	
Food temperature			
Low	1739 (11·45)	607 (13·26)	0·01*
High	13,453 (88·55)	3969 (86·64)	
Eating speed			
Slow	2373 (15·62)	887 (19·38)	<0·01*
Fast	12,819 (84·38)	3689 (80·62)	
Ingestion of leftover food			
No	9750 (64·18)	2396 (52·36)	<0·01*
Yes	5442 (35·82)	2180 (47·64)	
SDA detected within 1 year			
No	15,069 (99·19)	4520 (98·78)	0·03*
At screening	113 (0·74)	52 (1·14)	
Interval cancer within 1 year	10 (0·07)	4 (0·08)	

***Table 1*: Selected demographic characteristics and life-style variables among subjects in the training set and the validation set.**

[a] Number of ESCC cases in family members within 3 generations.

* *P*-values reached a significance level of 0.05.

target subjects (as in the current population-level screening program in China), the detection rates in both cohorts were ~1·7 fold of that for universal screening (Table 3). When only a small number of endoscopies were affordable, detecting as many SDA patients as possible must be the priority. In this case, the population coverage could be set to only 10%, and detection rates would reach up to 3·42 folds (from 0·81% to 2·76%) and 2·15 folds (from 1·22% to 2·63%) in the training and validation cohorts, as compared to universal screening (Table 3). The number of endoscopies required for detection of one case would be decreased from 124 to 36 in the training cohort, and from 82 to 38 in the validation cohort.

Sensitivity analysis

We developed a series of prediction models using different time windows to define interval cancers. The structure of the prediction model remained consistent until the time window was extended out to 2 years (Supplementary Table 1). For the strategy to model the nonlinear effects of the age variable, we found models with quadratic terms of age resulted in smaller AICs than the restricted cubic spline (Supplementary Table 2).

Discussion

Esophageal cancer screening in China is an undertaking of great magnitude in view of the huge population size

Predictors [a]	Total (*N* = 15,192)	Case (*N* = 123)	Univariate coefficients (95% CI)	Multivariate coefficients (95% CI)
Age (continuous)	58 (50, 63)	63 (60, 66)	0·14 (0·11, 0·18)	0·77 (0·11, 1·52)
Age^2	—	—	1.19*10 $^{-3}$ (9.20*10 $^{-4}$, 1.47*10 $^{-3}$)	−0·01 (−0·01, 0·00)
Family history of ESCC [b]	0 (0, 0)	0 (0, 0)	0.51 (0·23, 0·75)	0·58 (0·30, 0·82)
BMI (kg/m^2)				
>22	12,462 (82·03)	90 (73·17)	Ref	ref
<=22	2730 (17·97)	33 (26·83)	0.52 (0·11, 0·91)	0·40 (−0·01, 0·80)
Use coal or wood as main cooking fuel				
No	7505 (49·40)	39 (31·71)	Ref	ref
Yes	7687 (50·60)	84 (68·29)	0·75 (0·38, 1·14)	0·39 (0·01, 0·79)
Eating speed				
Slow	2373 (15·62)	11 (8·94)	Ref	ref
Fast	12,819 (84·38)	112 (91·06)	0·64 (0·06, 1·32)	0·82 (0·24, 1·50)
Ingestion of leftover food				
No	9750 (64·18)	64 (52·03)	Ref	ref
Yes	5442 (35·82)	59 (47·97)	0·51 (0·15, 0·86)	0·47 (0·11, 0·83)
Constant	—	—	—	−33·22 (−56·10, −13·45)

***Table 2*: Structure of the prediction model for predicting ESCC within 1 year based on 15,192 subjects enrolled from the screening arm of the ESECC trial.**

[a] Age, gender, family history of ESCC, BMI, cigarette smoking, alcohol drinking, unhealthy dietary habits, ESCC related symptoms, use of coal or wood as main cooking fuel, exposure to fumes in the kitchen, source of drinking water and pesticide exposure were included in a 2-step variable selection method. Variables were first evaluated in the univariate logistic regression model, and variables with odds ratio (OR) >1.3 and P-value<0.5 were subjected to multivariate logistic regression model for further selection. The structure of the final prediction model was determined by the Akaike Information Criterion (AIC). Only variables included in the final prediction model are shown in this Table.

[b] Number of ESCC cases in family members within 3 generations.

Proportion of high-risk subjects (%)	Training Set (15,192 subjects, 123 cases)				Validation Set (4576 subjects, 56 cases)			
	No. high-risk subjects	No. SDA	No. endoscopies per case	Detection rate ratio	No. high-risk subjects	No. SDA	No. endoscopies per case	Detection rate ratio
100	15,192	123	124	ref	4576	56	82	ref
90	13,672	123	111	1·11	4118	53	78	1·05
80 [a]	12,152	122	100	1·24	3660	53	69	1·18
70	10,633	120	89	1·39	3202	51	63	1·30
60	9114	117	78	1·59	2744	50	55	1·49
50 [b]	7595	105	72	1·71	2286	47	49	1·68
40	6076	99	61	2·01	1828	41	45	1·83
30	4557	85	54	2·30	1371	35	39	2·09
20	3038	62	49	2·52	914	25	37	2·24
10 [c]	1519	42	36	3·42	457	12	38	2·15

***Table 3*: Application performance of the established model in different scenarios in the training set and the validation set.**

[a] scenario 1, 80% population coverage for endoscopic screening.

[b] scenario 2, 50% population coverage for endoscopic screening.

[c] scenario 3, 10% population coverage for endoscopic screening.

in areas high-risk for ESCC, the high cost of endoscopy, and the poor acceptance of this invasive examination. Using a simple questionnaire-based tool to enrich for high-risk individuals before embarking on endoscopic examination is most probably the way of coming to grips with this problem.

Since detecting early malignant lesions in a general population is the primary goal of screening, a "good" risk prediction model should be built upon large-scale community-based screening cohorts which provide good representation of target populations and accurate identification of prevalent cases through the examination per se. To date, four questionnaire-based prediction models have been established for identification of individuals who are at high-risk for ESCC.[11,18–20] We note there is only one study other than our study which has constructed a community-based prediction model for ESCC.[18] However, in that study, endoscopic screening covered only a small proportion of enrolled participants, and ESCC cases were identified through cancer registry

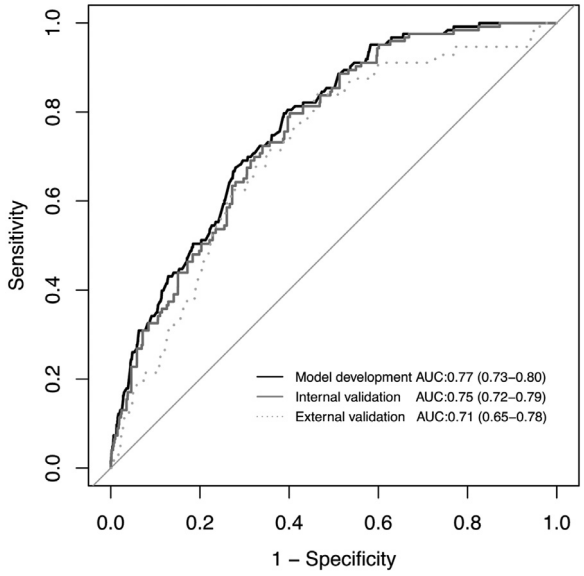

Figure 1. Receiver operating characteristic (ROC) curves of the risk prediction model for ESCC in the training, internal validation and external validation cohorts

This figure showed ROC curves of the risk prediction model for ESCC in the training, internal validation and external validation cohorts, respectively. Area under the curves (AUCs) were also calculated to quantify the performance of the risk prediction model in discriminating high-risk individuals for ESCC. The AUC during the model development was 0·77 (95% CI: 0·73–0·80), and leave-one-out cross-validation generated a slightly lower AUC of 0·75 (95% CI: 0·72–0·79). When applied to the external validation cohort, the prediction model still showed ideal performance, with an AUC of 0·71 (95% CI: 0·65–0·78).

Abbreviations: AUC, area under the curve; CI, confidence interval; ESCC, esophageal squamous cell carcinoma; ROC, receiver operating characteristic.

within 3 years after enrollment. Moreover, this method does not correctly identify prevalent SDA cases from the population under study.[18]

We previously constructed a community-based prediction model which took only SDAs detected under endoscopy as prevalent cases. As a growing body of real-world evidence had shown that interval cancers within a short time were probably prevalent cases which were "under-estimated" at screening,[12,13] we updated two aspects of our previous prediction model.

First, to accurately identify prevalent cases, cancers diagnosed within a relatively short time after screening were included. These cancers were very likely prevalent cases, as has been reported in endoscopic screening of esophageal adenocarcinoma and colorectal cancer.[12,13] This was due to several factors including, but not limited to the representativeness of the biopsy, sampling error in the production of pathology slides, and uncertainty regarding the pathologic diagnosis. In this study, we adopted a 1-year time window and combined these interval cancers with cases detected by screening as outcome events. We note that in our updated model, the predicted risk of 8 out of 10 interval ESCC cases in the training set was increased as compared with our previous model (Supplementary Figure 2). This redefinition of predicted outcome ensures a more accurate identification of prevalent cases in a defined population and avoids the problem of "under-estimated diagnosis" in once-only screening settings.

Second, since age is the strongest predictor for SDA lesions of the esophagus and its effect on risk is not linear, the method by which regression models are fitted should be reconsidered. Our previous age-stratified prediction model has demonstrated that the effect of age in predicting risk of ESCC among subjects aged 45–60 is much higher than that of individuals of 61–69[11]; however, the role of age was still linearly fitted within each subgroup (Supplementary Figure 3). To fit the non-linear effect of age, introducing a quadratic term or a restricted cubic spline in the model is a commonly used approach.[21–25] In the current study, we re-fitted the dynamic role of age using a quadratic term, which gradually weakened the effect of the age variable with increasing age (Supplementary Figure 3). Compared to our previous risk prediction model, fitting a whole age (45–69 years) model by adding a quadratic term of age will help solve the problem of interpreting the gap of predicted risk for subjects at the borderline of two age subgroups.

For this updated model, we also validated its performance in an external screening cohort with marked heterogeneity in demographic characteristics, risk behaviors and detection rate of SDA (Table 1), and an ideal discrimination ability was achieved. This ensures the generalizability of our risk stratification tool when used in real-world screening programs.

For the application of our model in real-world screening, we would like to make the following recommendations. When resources are not limited, we recommend screening the top 80% of high-risk individuals, where high sensitivities of 99·19% and 94·64% were achieved in the training and validation cohorts. If our model is integrated into the current ESCC screening program in China (required population coverage of 50% for endoscopic screening), a ~1·7 folds increase in detection rate as compared to universal screening can be achieved. Finally, in the setting of resource scarcity, detecting as many cancer patients as possible must be the priority. In such cases, we recommend a relatively high-risk probability cutoff to select the small proportion of individuals at highest risk to undergo endoscopy which will amount to 10% of individuals. The detection rate of SDA can then be increased by nearly 2–3·5 folds as compared to universal screening, which means the cost of per case detection can be reduced by 50%–70%.

There is a limitation in this study which should be noted. The training and external validation cohorts were both selected from populations in the Chinese high-risk rural are as, hence the effectiveness of the risk

prediction model presented in this study in non-high-risk areas or other countries/regions requires further studies to corroborate.

In summary, this study updated and validated an easy-to-use risk prediction model to identify individuals at high-risk of ESCC for endoscopic screening. This precision screening strategy would thereby raise the detection rate, achieving a comparable effectiveness with a much lower cost. Since all predictors in this model are available through a quick questionnaire survey, with the rapid development of mobile network and social media, this risk assessment tool can be easily installed in mobile terminals and disseminated among target populations to facilitate self-evaluation and management of the risk of ESCC. This novel decentralized strategy would have great potential to significantly improve the extensibility and sustainability of cancer screening, which are the key challenges facing the current government-initiated cancer prevention projects in China and most parts of the world.

Declaration of interests

The authors declare that they have no competing interests.

Contributors

Study concept and design: Y.K., Z.H. and M.L.; acquisition of data: C.G., M.L., R.X., F.Z., A.L., H.Y., F.L., L.D., L.S., Q.W., Z.L., H.Z., H.T., F.L., Y.L., Y.P., Z.H., H.C., and H.C.; analysis and interpretation of data: R.Z., M. L., Z.L., Z.H., and Y.K.; drafting of the manuscript: M. L., Z.H., Z.L. and R.Z.; statistical analysis: R.Z. and M. L.; study supervision: Y.K., and Z.H.. Y.K. and Z.H. has verified the underlying data, and all authors have full access to all the data in the study and accept responsibility to submit for publication.

Data sharing statement

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101394.

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