A Novel Clinical Model for Predicting Malignancy of Solitary Pulmonary Nodules: A Multicenter Study in Chinese Population

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Abstract

Background

This study aimed to establish and validate a novel clinical model to differentiate between benign and malignant solitary pulmonary nodules (SPNs).

Methods

Records from 406 patients with SPNs in Sun Yat-sen University Cancer Center were retrospectively reviewed. The data was randomly divided into training cohort and internal validation cohort. Other 190 SPNs patients in Henan Tumor Hospital were used for external validation. The novel prediction model was established using LASSO logistic regression analysis by integrating clinical features, radiologic characteristics and laboratory test data, the calibration of model was analyzed using the Hosmer-Lemeshow test (HL test). Subsequently, the model was compared with PKUPH and Mayo models using receiver-operating characteristics curve (ROC), decision curve analysis (DCA), net reclassification improvement index (NRI), and integrated discrimination improvement index (IDI) with the same data.

Results

A total of 15 variables were screened out and then aggregated to generate new prediction model. The model showed good calibration with the HL test (P = 0.221). The AUC for our model was 0.799, which was higher than other two reported models. DCA also showed our model was superior to the other two reported models. In our model, sensitivity = 70.06%, specificity = 77.08%. Compared with the PKUPH and Mayo models, the NRI of our model increased by 0.301 and 0.469 respectively, and the IDI improved 0.011 and 0.123, respectively. Furthermore, the model was significant positive correlation with PKUPH and Mayo models.

Conclusions

The novel model in our study had a high clinical value in diagnose of MSPNs.

Background

Solitary pulmonary nodules (SPNs) is a term used to describe single, round, well-circumscribed radiological opacity less than 3 cm in diameter[1]. With the widespread use of low-dose computed tomography (LDCT) screening for lung cancer, a frequently reported incidence of SPNs has shown a significantly increasing trend in recent years[2]. The detection rate of SPNs has increased from 8% to 51%[3]. In the SPNs cases, malignant SPNs (MSPNs) account for less than 10% of these nodules[4]. And the National Lung Screening Trial (NLST) found that although the rate of SPNs positivity was 25%, but 96% of the nodules evaluated in that study were benign SPNs (BSPNs)[5]. The LDCT screening, in turn, gives rise to a high number of false positive results. So, correctly identification and diagnosing MSPNs is becoming more and more important. Early diagnosis and treatment of MSPNs greatly improves the overall survival rate and prognosis of patients with lung cancer[6].

Traditionally, preoperative assessment of SPNs was based on clinicians' and radiologists' personal experience. Therefore, the clinical experience and judgment may not be reproducible or reliable. To overcome this issue, researchers have developed some clinical mathematical prediction models based on clinical features, or radiologic characteristics, or serum markers to diagnose MSPNs. The widely used prediction model for screening SPNs include the Mayo Clinic model[7], the Department of Veterans Affairs (VA) model[8], Peking University People's Hospital (PKUPH) model[9], and the Bayesian Inference Malignancy Calculator (BIMC) model[10]. Although the four models are different from one

another in the features that are considered as predictive factors. However, they are all developed based on clinical and imaging features.

Recently, some laboratory test data are widely used in cancer management to aid lung cancer diagnosis. Pulmonary function test (PFT) is often considered the basis for diagnosis in many categories of pulmonary disease[11]. The impaired lung function is associated with increased risk of lung cancer[12]. Serum biomarkers are easily accessible, which are widely used to aid the traditional imaging techniques to enhance the early diagnosis of lung cancer. Serum tumor markers such as cytokeratin 19 fragment (Cyfra21-1) and carcinoembryonic antigen (CEA) are commonly used to screen for lung cancer, disease monitoring and prognosis, which are recommended by both the National Academy of Clinical Biochemistry (NACB) and European Group on Tumor Markers (EGTM)[13]. In the last years, serum microRNAs (miRNAs) had been demonstrated to have an important role in tumor microenvironment and immune regulation, miRNAs could be used as a diagnostic and prognostic tool for lung cancer[14].

Until now, combine clinical features with radiologic characteristics and laboratory test data to differentiate between BSPNs and MSPNs was not reported. Multiple laboratory tests detecting, and combined analysis of clinical features and traditional imaging are a novel approach for noninvasive detection of lung cancer. Hence, the aim of this study is to construct a novel clinical model, incorporating clinical features, radiographic characteristics and laboratory test data, to identify and diagnose MSPNs in patients with SPNs. And assess its incremental value to the PKUPH model and Mayo model for individual MSPNs estimation.

Materials And Methods

Patient selection and data collection

We performed a retrospective analysis of SPNs patients were recruited from Sun Yat-sen University Cancer Center (Guangzhou, China) between Jan 2011 to Dec 2016. The data was randomly divided into training cohort and internal validation cohort. The training cohort was used to constructed a novel model for predicting malignancy of SPNs. Addition patients with SPNs recruited in Henan Tumor Hospital (Zhengzhou, China) from Jan 2013 to Jun 2018 were used as an external validation cohort. All patients provided written informed consent to research use. This study was approved by the Hospital Ethics Committee in Sun Yat-sen University Cancer Center and Henan Tumor Hospital. This study was conducted according to the Declaration of Helsinki. The inclusion criteria were the following: a: all patients were selected based on presence of SPNs on chest CT scan. Final diagnoses were confirmed with histopathologic diagnosis based on tissue obtained from CT-guided transthoracic needle biopsy, bronchoscopy, thoracoscopy, or surgical resection; b: $\leq$ 3 cm diameter solitary pulmonary nodules lesion in the lung; c: no extrapulmonary malignancy; d: complete clinical, CT image, and laboratory data, and all the data were collected at diagnosis prior to any treatment. The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn), with the approval RDD number as RDDA2020001625.

Clinical features, radiologic characteristics and laboratory test data

Clinical features were collected from the selected patients, including age of the patient, gender, height, weight, body mass index (BMI), smoking history, family history of cancer, symptoms (fever, cough, expectoration, sputum with blood, hemoptysis, and chest pain). radiologic characteristics including tumor site (left lobe or right lobe, upper, middle or lower), radiographic characteristics including SPNs diameter, SPNs area, calcification, cavity, spiculation, mediastinal or hilar lymphadenopathy, pleural thickening, pleural adhesion, pleural stretch, and pleural effusion. Laboratory test data including lung function indices (vital capacity (VC), forced expiratory volume in one second (FEV1), FEV1%, FEV1/FVC, RV/TLC, diffusion capacity for carbon monoxide (DLCO), and DLCO%,) and blood-based biomarkers (white blood cell

(WBC), neutrophil (N), lymphocyte (L), monocyte (M), platelets (PLT), neutrophil/lymphocyte ratio (NLR), derived NLR (dNLR)[15]: dNLR = N/(WBC - N), lymphocyte/monocyte ratio (LMR), platelet/lymphocyte ratio (PLR), systemic immune-inflammation index (SII)[16]: SII = (PLT × N)/L, red blood cell (RBC), Hemoglobin (Hbg), alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALT/AST ratio (LSR), total protein (TP), albumin (ALB), globulin (GLOB), ALB/ GLOB ratio (AGR), total bile acid (TBA), total bilirubin (TBIL), direct bilirubin (DBIL), γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), C-reactive protein (CRP), prognostic nutritional index (PNI)[17]: PNI = ALB (g/L) + 5 × lymphocyte count × 10^9/L, creatinine (CRE), cystatinC (Cys-C), fibrinogen (FBG), cytokeratin 19 fragment (Cyfra21-1), carcinoembryonic antigen (CEA), and neuron-specific enolase (NSE)).

Statistical analysis

All statistical analyses were performed using SPSS software, version 19.0 (SPSS Inc., Chicago, IL, USA) and R software version 3.6.1 (http://www.R-project.org). A least absolute shrinkage and selection operator (LASSO)[18] regression was used in the training cohort for the potential predictors to select the probability of malignant SPNs (MSPNs). The novel prediction model for predicting MSPNs was established based on the results of the LASSO regression analysis. The prediction model was evaluated on discrimination and calibration. Discrimination was assessed using receiver operating characteristic (ROC) curves were used to assess the overall discrimination ability of our model and to choose its best diagnosis cut-off value[19]. Calibration reflects the agreement between predicted probabilities from the model and observed outcomes. We used the Hosmer-Lemeshow goodness-of-fit test (HL test) to statistically determine the extent of agreement between the predicted and observed probabilities[20]. To evaluate whether the new model was informative beyond PKUPH model, and Mayo model. We performed area under the ROC curve (AUC), decision curve analysis (DCA)[21], net reclassification improvement index (NRI)[22], and integrated discrimination improvement index (IDI)[22] to quantify the predictive power and the added predictive ability of our model. Nomogram (by the package of rms in R) was developed to enhance the use of our model in predicting malignancy of SPNs by combining our model, PKUPH model, and Mayo model. Its performance was assessed by calibration curve in internal validation with bootstrapping (1000 bootstrap resamples)[23]. Pearson's correlation coefficient was used to identify the relationship between our model, PKUPH model, and Mayo model[24]. The difference was considered statistically significant when a P-value was less than 0.05.

Data availability

The data are not available for public access because of patient privacy concerns but are available from the corresponding author on reasonable request approved by the institutional review boards of Sun Yat-sen University Cancer Center and Affiliated Tumor Hospital of Zhengzhou University.

Results

Characteristics of the training and validation cohorts

In total, 596 SPNs patients were included in this retrospective study, including 406 patients from Sun Yat-sen University Cancer Center. Clinical, CT image, and laboratory data were presented in Supplement table 1. The data was randomly divided into training cohort (n=273) and internal validation cohort (n=133). And other 190 patients from Henan Tumor Hospital were used for external validation (Supplement table 2). The mean age (SD) of patients in the training cohort was 58.1 (10.0) years; 189 patients (69.2%) were men and 177 (64.8%) patients were diagnosed as MSPNs, including 148 (83.6%) adenocarcinoma, 20 (11.3%) squamous cell carcinoma and 9 (5.1%) others. In the internal validation cohort, the amounts for adenocarcinoma, squamous cell carcinoma, and others were 70 (81.4%), 13 (15.1%), and 3

(3.5%), respectively, and in the external validation cohort, the amounts for adenocarcinoma, squamous cell carcinoma, and others were 102 (81.6%), 16 (12.8%), and 7 (5.6%), respectively.

Predictors selection

To select the potential predictors for predicting malignancy of SPNs, we used LASSO logistic regression analysis. Figure 1A showed the change in trajectory of each variable was analyzed. Moreover, 10-fold cross-validation was employed for model construction, and the confidence interval under each λ was presented in Figure 1B. According to the 1-SE criteria, we selected λ = 0.037 as the optimal value for the model, which included 15 potential predictors (gender, age, fever, chest pain, diameter, calcification, pleural thickening, pleural adhesion, VC, FEV1, DLCO1, LSR, TBA, CEA, and NSE) with non-zero coefficients from the 63 candidate variables identified in the training cohort, and their coefficients were presented in Figure 1C. The clinical and laboratory data of these selected predictors in training cohort, validation cohort, and external validation cohort were presented in Table 1.

Construction and evaluation of the novel prediction model

For predicting each individual patient's malignancy risk, the risk score was calculated for each patient with the following formula:

Risk score = -1.014 - (0.131* gender) + (0.025*age) - (0.281*fever) - (0.257*chest pain) + (0.306*diameter) - (0.793*calcification) - (0.188*pleural thickening) + (0.18*pleural adhesion) - (0.227*VC) - (0.083*FEV1) + (0.036*DLCO1) - (0.045* LSR) - (0.006* TBA) + (0.026*CEA) + (0.037*NSE).

Subsequently, we used the following formulas to calculate the probability of malignancy: probability (P) = $e^{\text{risk score}}$ /(1+$e^{\text{risk score}}$), where e is the natural logarithm, the values for the continuous variables were medical recorded; gender = 1 if the patient was male (otherwise = 0); the value for the fever, chest pain, calcification, pleural thickening, pleural adhesion, equals 1 if the element exists, and 0 otherwise.

Finally, the calibration of model was analyzed using HL test. The new prediction model showed good calibration with the HL test (χ2 = 10.673, P = 0.221, Supplement Figure 1A). The AUC for the novel model was 0.799 (95% CI: 0.746 - 0.845), a P value of 0.64 was ultimately selected as a cut-off point and P values > 0.64 should be considered a malignant disease. The sensitivity of this model for the training cohort was 70.06% (62.7%-76.7%), specificity = 77.08% (67.4%-85.0%), positive likelihood ratio (LR+) = 3.06, and negative likelihood ratio (LR-) = 0.39.

Validation of the novel prediction model

The performance of the novel prediction model was validated in the internal validation cohort and external validation cohort. According to the formula constructed in the training cohort, a risk score and probability of malignancy were calculated for each patient in the validation set. Then the discrimination and the calibration of the model were assessed using ROC, calibration curve, and the HL test were performed. For the internal validation cohort, the AUC was 0.803 (95% CI: 0.726 - 0.867). The probability of malignancy with a cut-off point of 0.64, the sensitivity, specificity, LR+, and LR- of model was 68.60%, 74.47%, 2.69, and 0.42. For the external validation cohort, the AUC was 0.719 (95% CI: 0.650 - 0.782), the sensitivity, specificity, LR+, and LR- of model was 76.80%, 49.23%, 1.51, and 0.47. In addition, calibration curve and HL test reflected the new model had a high accuracy of the model for predicting MSPNs both in the internal validation cohort (χ2 = 8.127, P = 0.421, Supplement Figure 1B) and external validation cohort (χ2 = 12.04, P = 0.149, Supplement Figure 1C).

Assessment the performance of our model, PKUPH model, and Mayo model for SPNs screening using ROC analysis, DCA, NRI and IDI

The data for training, validation and external validation cohorts were substituted into our proposed model, PKUPH model and Mayo model to generate the respective ROC curves (Figure 2 and Table 2). For the training cohort, the AUC of the three models was 0.799, 0.616, and 0.524, respectively. The AUC of our model was significantly higher than the PKUPH model and Mayo model (P < 0.001). For the internal validation cohort, the AUC of the three models was 0.803, 0.725, and 0.691, respectively. The AUC of our model was significantly higher than the PKUPH model (P = 0.042) and Mayo model (P = 0.026). For the external validation cohort, the AUC of the three models was 0.719, 0.641, and 0.575, respectively. The AUC of our model was also significantly higher than the PKUPH model (P = 0.049) and Mayo model (P = 0.004).

DCA was employed to evaluate the clinical utility of the three models in the training, validation and external validation cohorts (Figure 3). The x-axis of the decision curve was the threshold of the predicted probability using the models to classify MSPNs patients and BSPNs patients. The y-axis shows the clinical decision net benefit for patients based on the classification result in this threshold. The decision curves of the treat-all scheme and the treat-none scheme were used as references in the decision curve analysis. Our model (red) showed had a higher overall net benefit than PKUPH model (black) and Mayo model (blue) both in training, validation and external validation cohorts. The application of our model was associated with reasonably good clinical utility across the three data.

The improvement in the predictive accuracy of our proposed model as compared to the PKUPH model and Mayo model, which was estimated by calculating the NRI and IDI in the training, validation and external validation cohorts (Table 3). Comparing our model to PKUPH model and Mayo model, the changed in NRIs of the training, validation and external validation cohorts were 0.301 (P < 0.001) and 0.469 (P < 0.001), 0.155 (P = 0.094) and 0.454 (P < 0.001), 0.002 (P = 0.980) and 0.063 (P < 0.001), respectively. The improved in IDIs of the training, validation and external validation cohorts were 0.011 (P = 0.679) and 0.123 (P < 0.001), -0.035 (P = 0.326) and 0.119 (P < 0.001), -0.042 (P = 0.198) and 0.246 (P < 0.001), respectively. These results indicated that the new model could supplement the deficiencies of the two models in predicting MSPNs.

Comparison of the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio of the three models analyzed in this study

Comparison of the sensitivity, specificity, LR+, LR- of the three models in the three independent cohorts of patients (Supplement Table 3). The threshold of our model was 0.64, and the threshold of PKUPH model and Mayo model were used literature reports as 0.463 and 0.10, respectively. In the training cohort, the performance of our model were: sensitivity: 70.06% (95% CI: 62.7%-76.7%); specificity: 77.08% (95% CI: 67.4%-85.0%); LR+: 3.06 (95% CI: 2.6-3.5); and LR-: 0.39 (95% CI:0.3-0.6); for PKUPH model, sensitivity was 85.88% (95% CI: 79.9%-90.6%), specificity was 30.21% (95% CI: 21.3%-40.4%); LR+: 1.23 (95% CI: 0.9-1.7); and LR-: 0.47 (95% CI: 0.3-0.7); for Mayo model, sensitivity was 22.03% (95% CI: 16.2%-28.9%), specificity was 79.17% (95% CI: 69.7%-86.8%); LR+: 1.06 (95% CI: 0.8-1.4); and LR-: 0.98 (95% CI: 0.7-1.5). The specificity, LR+, and LR- of our model were better than PKUPH model, whereas the sensitivity was lower than PKUPH model, and the sensitivity, LR+, and LR- of our model had a good performance than Mayo model, but the specificity was worse than Mayo model. There had inconsistent results in the validation and external validation cohorts. Comparison of the three models at their respective thresholds in the three cohorts were inconclusive: each model has its own merits and demerits in predicting MSPNs.

Building and validating combined predictive nomogram

In order to combine the merits of each model in predicting MSPNs, a combined nomogram was constructed from our model, PKUPH model, and Mayo model, to predict malignancy of SPNs in training cohort, validation cohort, and external validation cohort (Figure 4A, B, C, respectively). Each model was assigned a point. As an example, locate our model risk

score, draw a line straight upward to the "Points" axis to determine how many points associated with that model risk score. Repeat the process for each model, sum the points achieved for each covariate, and locate the sum on the "Total Points" axis. Final draw a line straight down to find the patient's risk of malignance. The AUC of combined nomogram was 0.806 for the training set, an AUC of 0.819 for the validation set, and an AUC of 0.7193 for the external validation set, which were higher than those models alone. Then the calibration curves for the probability of malignancy were used to assess the agreement between the predicted and actual observation in training cohort, validation cohort, and external validation cohort (Figure 4D, E, F, respectively). The calibration plots showed a good match between the prediction by nomogram and actual observation. All the results revealed the improvement of SPNs discrimination using the combined nomogram.

The correlation between the novel prediction, PKUPH, and Mayo models

Figure 5 and Supplement Table 4 showed the correlations between the novel prediction model, PKUPH model, and Mayo model in training cohort (A), internal validation cohort (B) and external validation cohort (C). Pearson's correlation coefficients (PCC) was computed to determine the interrelationship between the three models. The results revealed that the new prediction model was significantly and positively correlated with PKUPH model (PCC: training cohort: 0.571, $P < 0.001$; internal validation cohort: 0.689, $P < 0.001$; external validation cohort: 0.645, $P < 0.001$) and Mayo model (PCC: training cohort: 0.213, $P < 0.001$; internal validation cohort: 0.373, $P < 0.001$; external validation cohort: 0.278, $P < 0.001$), indicating that our analysis results had credible prediction value.

Discussion

In this study, we conducted retrospective analysis of individual clinical features, image and laboratory data of 596 newly diagnosed SPNs patients in two cancer centers. Then a novel prediction model in predicting MSPNs was developed by using Lasso regression analysis. We compared the performance of the novel model with PKUPH model, and Mayo model. The identified novel prediction model successfully classified the SPNs patients into BSPNs and MSPNs, and the new model had better ability than the two existing models in predicting MSPNs. The results were also validated with internal validation and external validation cohorts, suggesting the reproducibility and reliability of the developed prediction model.

Using Lasso regression analysis, we found 15 predictors (gender, age, fever, chest pain, diameter, calcification, pleural thickening, pleural adhesion, VC, FEV1, DLCO1, LSR, TBA, CEA, and NSE) from 63 candidate variables. Among the predictors, gender[25], age[26], diameter[27], calcification[28], FEV1[12], CEA[29] and NSE[30] had been reported before. The remaining predictors that were identified in our study but not been reported in other studies, the probably because previously reported models did not incorporate these potential predictors for analysis. Thus, whether these predictors could really be used to predict MSPNs, which required more follow-up clinical studies to confirm the results.

We compared the predictive accuracy of the prediction model with PKUPH model, and Mayo model. ROC curve showed that the AUC of our model was significantly higher than PKUPH model and Mayo model all in training, internal validation and external validation cohorts. The DCA also showed our model was good performance in MSPNs prediction than other two models in the three cohorts. Compared to Mayo model, our model significantly improved the reclassification performance, both in the training cohort (NRI 0.469; $P < 0.001$; IDI 0.123; $P < 0.001$), and in the internal validation (NRI 0.454; $P < 0.001$; IDI 0.119; $P < 0.001$), and in the external validation cohort (NRI 0.063; $P < 0.001$; IDI 0.246; $P < 0.001$). And compared to PKUPH, for NRIs, our model was increased both in the three cohorts. For IDIs, our model was also increased in the training cohort except for slightly reduced in the internal validation and external validation cohorts. Therefore, these results may support the potential use of our model as a useful tool to help clinicians to identify and diagnose MSPNs in patients with SPNs.

Compared to the previous reported models, our study had several strengths. 1. Combined clinical features with radiologic characteristics and laboratory test data to differentiate between BSPNs and MSPNs had not been reported. This study was the first to establish a prediction model in predicting MSPNs by integrating clinical features, radiologic characteristics and laboratory test data, which could combine their individual advantages to achieve a better prediction model. 2. All models (Mayo model, VA model, and BIMC model) except the PKUPH model were developed using North American or European populations. In this retrospective study including 596 SPNs patients came from two cancer centers in China. The prediction model was developed in the training cohort from 63 candidate variables and validated in internal and external validation cohorts. Therefore, the advantages of our study were its large SPNs sample size and inclusion of a Chinese cohort. 3. The Lasso regression analysis was utilized to select predictors and build a prediction model. The method enabled to handle the multi-collinearity problems, screen overall variables, and adjust for model's over fitting and avoid extreme predictions. This statistical method could improve the predictive accuracy, and it had been applied in many research[31-33]. 4. Comparison the diagnostic accuracy and discriminative ability of the novel prediction model with PKUPH and Mayo models using multiple methods including ROC analysis, DCA, NRI and IDI in the same data, making it was credible evidence supporting our analysis results. 5. In order to combine the merits of the three models in predicting MSPNs, a combined easy-to-use nomogram was constructed from the three models, and the results showed the nomogram could improve the diagnostic accuracy and agreement in MSPNs and BSPNs, and then optimize treatment in this clinical setting.

There also had several drawbacks of this study should be considered. Firstly, this was a retrospective analysis and selection bias might exist. Secondly, the sensitivity and specificity of our model was not very high, in the future, we intend to incorporate molecular markers to develop a model that could improve sensitivity and specificity in identifying MSPNs among the SPNs. Thirdly, the blood-based predictive markers in this study included only common biomarkers in clinical routine laboratory testing while other potential predictive biomarkers such as miRNAs[34], genome-wide changes in DNA methylation[35], proteomic profile in serum[36], autoantibodies or tumor-associated antigens[37] were not evaluated. Finally, although this study was a multicenter study in Chinese population, further research was still needed to fully validate the model before it can be used to clinical application.

Conclusions

In summary, we had for the first time developed a novel prediction model by integrating clinical features, radiologic characteristics and laboratory test data, which was more accurate than two previously described models and was able to identify MSPNs from SPNs. In addition, incorporating the novel model, PKUPH model, and Mayo model into a nomogram could reinforce a diagnosis of MSPNs in patients with SPNs. Nevertheless, undertaking a prospective study to further validate the model for predicting MSPNs in a large population-based LDCT screening positive setting was required.

Abbreviations

AUC = the areas under ROC curve; BMI = body mass index; WBC = white blood cell; NLR = neutrophil/lymphocyte ratio; PLR = platelet/lymphocyte ratio; ALB = albumin; ALT = alanine transaminase; AST = aspartate aminotransferase; SLR = AST/ALT ratio; ALP = alkaline phosphatase; CRP = C-reactive protein; CAR = C-reactive protein/albumin ratio; LDH = lactic dehydrogenase; GGT = glutamyl transpeptidase; TBIL = total bilirubin; DBIL = direct bilirubin; PNI = prognostic nutritional index; PCC = Pearson's correlation coefficient; IQR = interquartile range; VC: vital capacity; FEV1: forced expiratory volume in one second; DLCO: diffusion capacity for carbon monoxide; CEA: carcinoembryonic antigen; NSE: neuron-specific enolase.

Declarations

Acknowledgments

None.

Authors' contributions

QXX, WLL, and SLC are senior authors who contributed in study design. XH, NX, and XHL selected patients for the study and collected clinical data. XMT, SGP, YYQ, and LNJ performed data analysis, XH and NX wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are not publicly available due to patient privacy concerns, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of Sun Yat-sen University Cancer Center and Henan Tumor Hospital, and all patients provided written informed consent at the first visit to our center.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Demographics and clinical characteristics of patients in the training and validation cohort

Characteristic	Training cohort n = (273)		Internal validation cohort n = (133)		External validation cohort n = (190)	
	Benignancy n = 96 No.(%) or Mean ± sd	Malignancy n = 177 No.(%) or Mean ± sd	Benignancy n = 47 No.(%) or Mean ± sd	Malignancy n = (86) No.(%) or Mean ± sd	Benignancy n = 65 No.(%) or Mean ± sd	Malignancy n = 125 No.(%) or Mean ± sd
Gender						
Male	75 (78.1%)	114 (64.4%)	33 (70.2%)	56 (65.1%)	42 (64.6%)	55 (44.0%)
Female	21 (21.9%)	63 (35.6%)	14 (29.8%)	30 (34.9%)	23 (35.4%)	70 (56.0%)
Age (years)	55.1 ± 10.8	59.8 ± 9.2	48.5 ± 11.6	60.1 ± 10.6	55.3 ± 9.9	59.8 ± 9.1
Fever						
Yes	6 (6.3%)	4 (2.3%)	0 (0.0%)	5 (5.8%)	4 (6.2%)	3 (2.4%)
No	90 (93.7%)	173 (97.7%)	47 (100.0%)	81 (94.2%)	61 (93.8%)	122 (97.6%)
Chest pain						
Yes	19 (19.8%)	20 (11.3%)	4 (8.5%)	11 (12.8%)	9 (13.8%)	16 (12.8%)
No	77 (80.2%)	157 (88.7%)	43 (91.5%)	75 (87.2%)	56 (86.2%)	109 (87.2%)
Diameter[a] (cm)	1.8 ± 0.7	2.1 ± 0.6	1.8 ± 0.6	2.3 ± 0.6	1.9 ± 0.7	2.0 ± 0.6
Calcification						
Yes	9 (9.4%)	3 (1.7%)	3 (6.4%)	2 (2.3%)	4 (6.2%)	6 (4.8%)
No	87 (90.6%)	174 (98.3%)	44 (93.6%)	84 (97.7%)	61 (93.8%)	119 (95.2%)
Pleural thickening						
Yes	20 (20.8%)	26 (14.7%)	11 (23.4%)	13 (15.1%)	11 (16.9%)	11 (8.8%)
No	76 (79.2%)	151 (85.3%)	36 (76.6%)	73 (84.9%)	54 (83.1%)	114 (91.2%)
Pleural adhesion						
Yes	13 (13.5%)	40 (22.6%)	12 (25.5%)	18 (20.9%)	19 (29.2%)	26 (20.8%)
No	83 (86.5%)	137 (77.4%)	35 (74.5%)	68 (79.1%)	46 (70.8%)	99 (79.2%)
VC (L)	3.6 ± 0.7	3.2 ± 0.8	3.7 ± 0.9	3.2 ± 0.7	3.1 ±0.8	2.8 ± 0.7
FEV1 (L)	2.8 ± 0.6	2.4 ± 0.7	3.0 ± 0.8	2.5 ± 0.6	2.6 ± 0.7	2.3 ± 0.6
DLCO (mmol/min/kpa)	5.8 ± 3.0	6.2 ± 2.9	6.0 ± 3.1	6.8 ± 7.4	6.6 ± 1.7	6.2 ± 1.4

TBA (umol/L)	5.8 ± 7.5	4.3 ± 3.6	4.0 ± 4.1	4.1 ± 3.2	7.0 ± 5.0	6.0 ± 4.3
LSR	1.2 ± 0.4	1.0 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	1.0 ± 0.4	1.0 ± 0.3
CEA (ng/mL)	2.7 ± 2.0	5.0 ± 7.9	2.5 ± 1.7	7.9 ± 14.3	2.3 ± 1.8	5.0 ± 12.9
NSE (ng/mL)	12.4 ± 4.0	13.8 ± 4.1	12.5 ± 4.3	12.6 ± 3.1	13.0 ±4.1	14.2 ± 4.4

a: The maximum diameter of SPNs;

Abbreviations: sd: standard deviation; VC: vital capacity; FEV1: forced expiratory volume in one second; DLCO: diffusion capacity for carbon monoxide; PLR : platelet/lymphocyte ratio; LSR: ALT/AST ratio; CEA: carcinoembryonic antigen; NSE: neuron-specific enolase.

Table 2. Comparison of the area under the ROC curves (AUCs) of three models analyzed in this study

Models	AUCs	95% CI	P value
For training cohort			
Our model	0.799	0.746 - 0.845	
PKUPH model	0.616	0.556 - 0.674	
Mayo model	0.524	0.463 - 0.585	
Our model vs PKUPH model			< 0.001
Our model vs Mayo model			< 0.001
For internal validation cohort			
Our model	0.803	0.726 - 0.867	
PKUPH model	0.725	0.641 - 0.799	
Mayo model	0.691	0.605 - 0.768	
Our model vs PKUPH model			0.042
Our model vs Mayo model			0.026
For external validation cohort			
Our model	0.719	0.650 - 0.782	
PKUPH model	0.641	0.569 - 0.709	
Mayo model	0.575	0.502 - 0.646	
Our model vs PKUPH model			0.049
Our model vs Mayo model			0.004

ROC: receiver operating characteristic; AUCs: areas under the curve; CI: confidence interval.

Table 3. The NRI and IDI were used to assess reclassification performance and improvement in discrimination of our novel prediction model.

	NRI	P Value	IDI	P Value
Training cohort				
Our model vs PKUPH model	0.301	< 0.001	0.011	0.679
Our model vs Mayo model	0.469	< 0.001	0.123	< 0.001
Internal validation cohort				
Our model vs PKUPH model	0.155	0.094	-0.035	0.326
Our model vs Mayo model	0.454	< 0.001	0.119	< 0.001
External validation cohort				
Our model vs PKUPH model	0.002	0.980	-0.042	0.198
Our model vs Mayo model	0.063	< 0.001	0.246	< 0.001

Abbreviations: NRI: net reclassification improvement index; IDI: integrated discrimination improvement index.

Figures

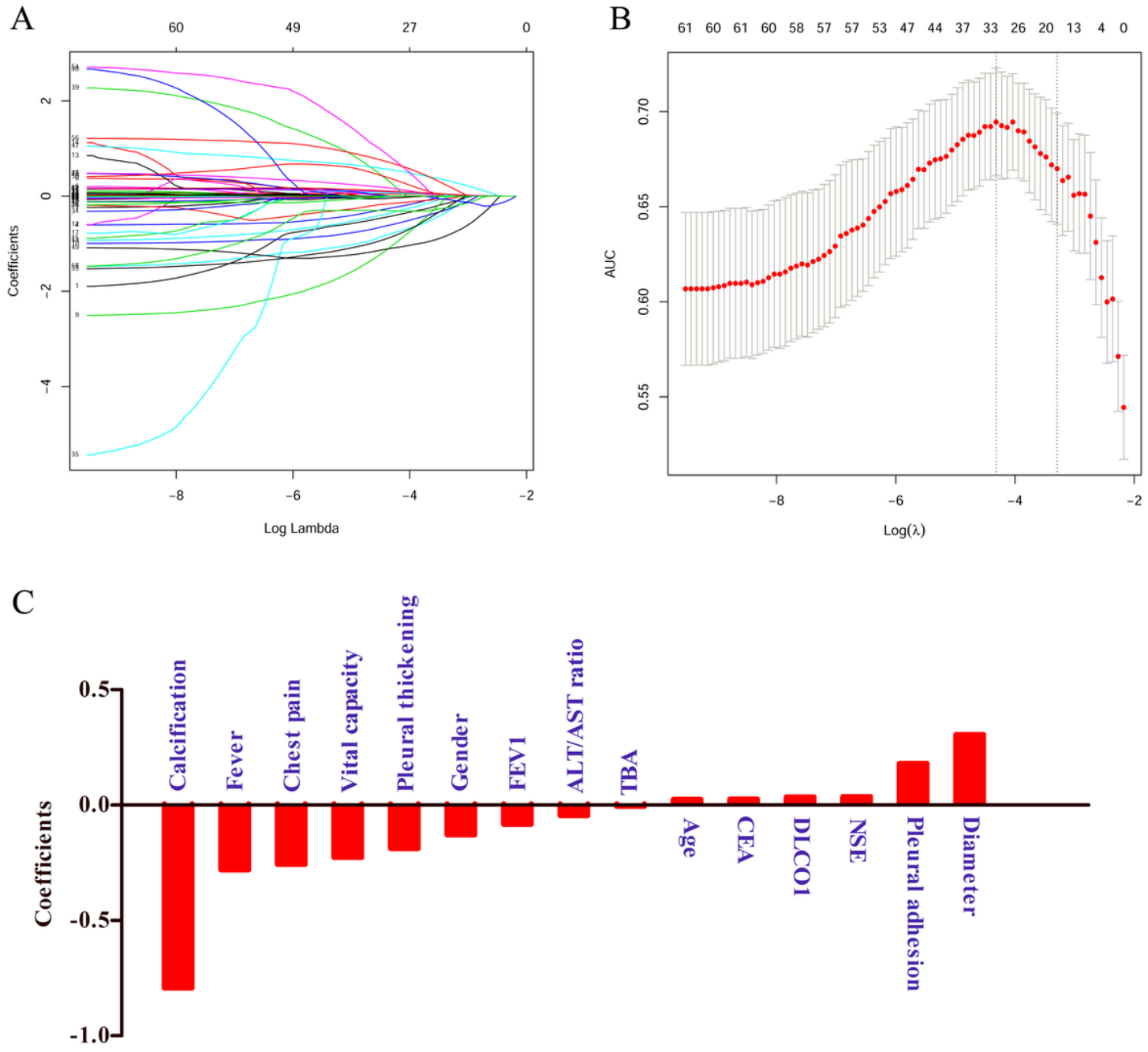

Figure 1

Potential predictors selection using LASSO logistic regression.

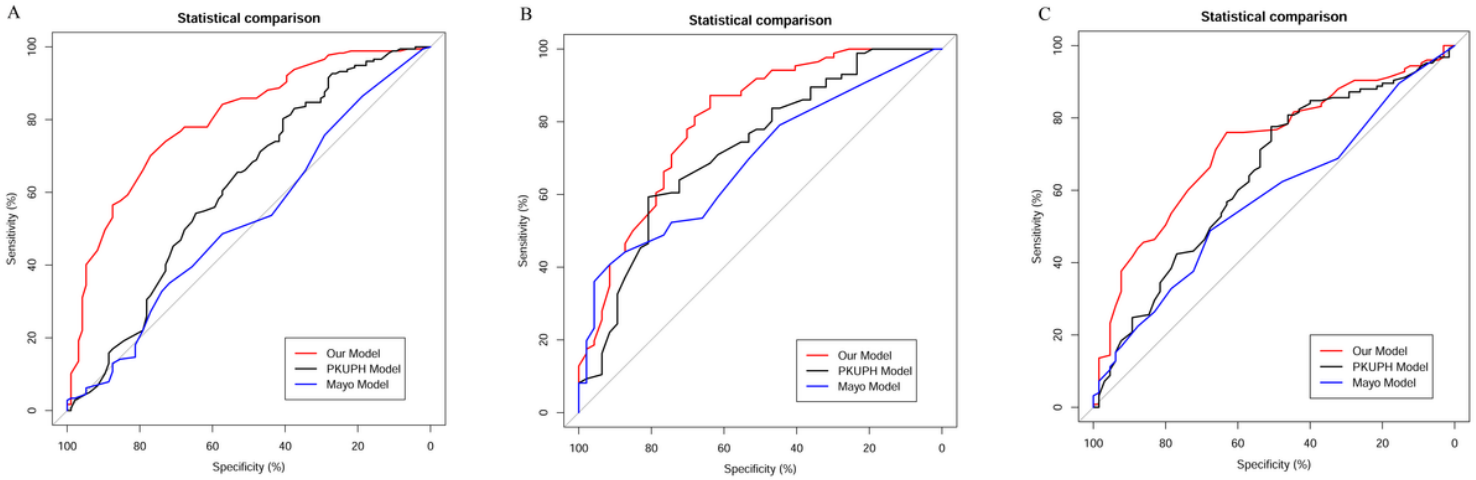

Figure 2

ROC comparison for the three models analyzed in training cohort (A), internal validation cohort (B) and external validation cohort (C), respectively.

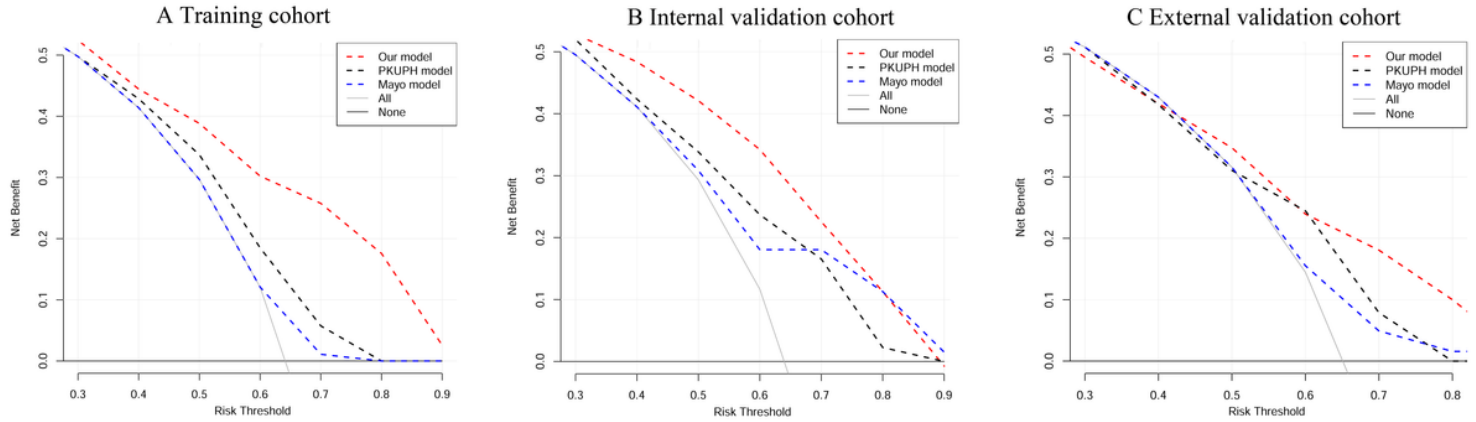

Figure 3

Decision curve analysis for the three models analyzed.

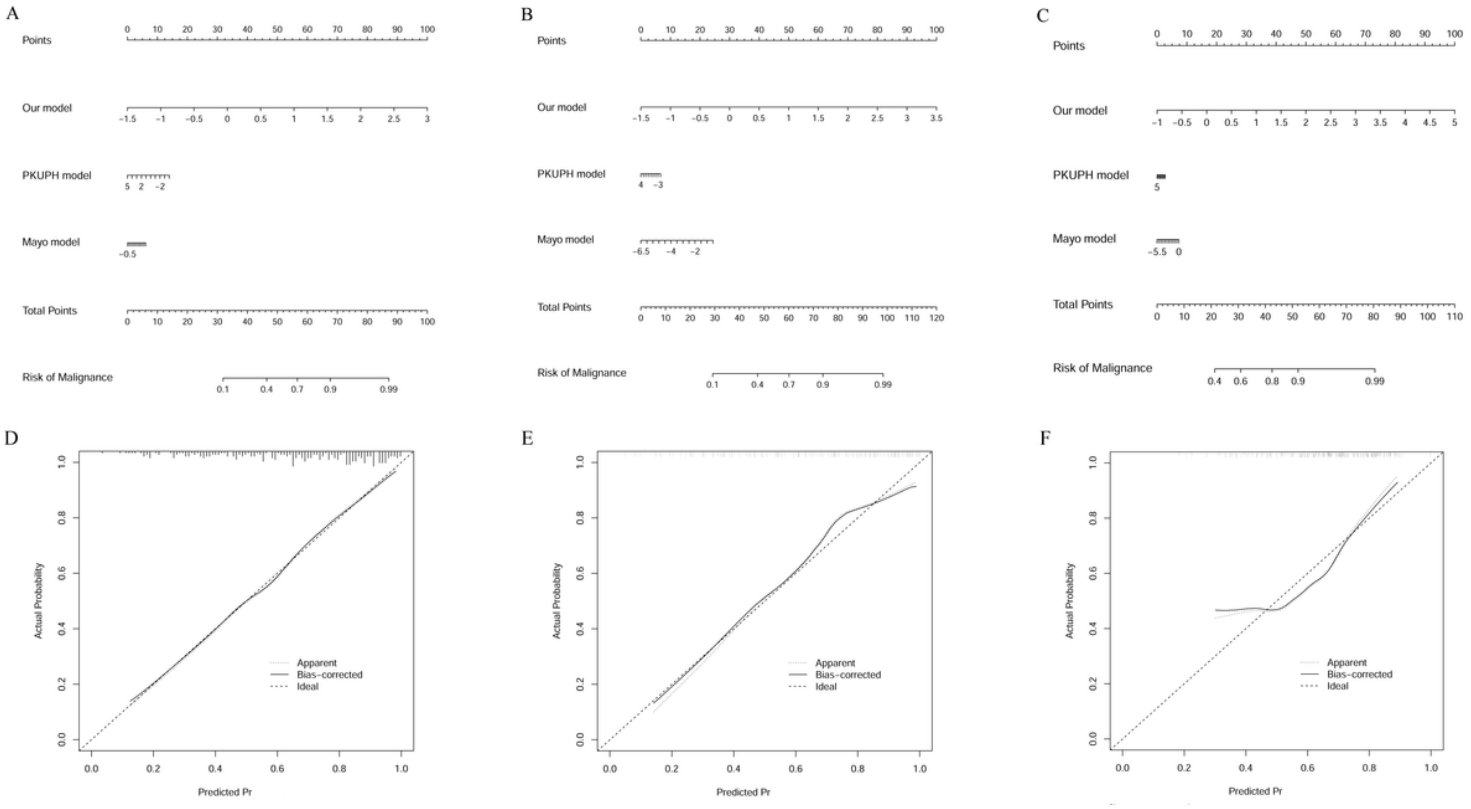

Figure 4

The nomograms (A, B, C) were used to estimate malignant SPNs, along with the calibration plot (D, E, F) for the nomograms in training cohort, internal validation cohort and external validation cohort, respectively.

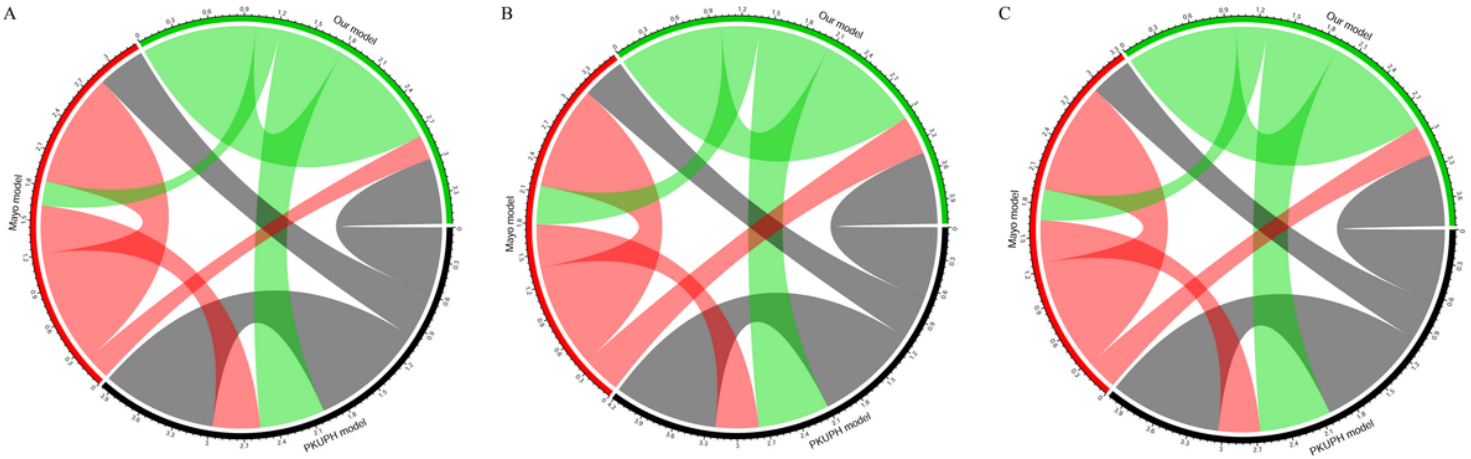

Figure 5

The correlations between our model, PKUPH model and Mayo model in training cohort (A), internal validation cohort (B) and external validation cohort (C), respectively.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx

- SupplementaryTable2.docx
- SupplementaryTable3.docx
- SupplementaryFigure1.tif
- SupplementaryTable4.docx