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A Clinical Model To Estimate the Pretest Probability of Lung Cancer in Patients With Solitary Pulmonary Nodules

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Abstract

Background—Estimating the clinical probability of malignancy in patients with a solitary pulmonary nodule (SPN) can facilitate the selection and interpretation of subsequent diagnostic tests.

Methods—We used multiple logistic regression analysis to identify independent clinical predictors of malignancy and to develop a parsimonious clinical prediction model to estimate the pretest probability of malignancy in a geographically diverse sample of 375 veterans with SPNs. We used data from Department of Veterans Affairs (VA) administrative databases and a recently completed VA Cooperative Study that evaluated the accuracy of positron emission tomography (PET) scans for the diagnosis of SPNs.

Results—The mean ($\pm$ SD) age of subjects in the sample was 65.9 ± 10.7 years. The prevalence of malignant SPNs was 54%. Most participants were either current smokers ($n = 177$) or former smokers ($n = 177$). Independent predictors of malignant SPNs included a positive smoking history (odds ratio [OR], 7.9; 95% confidence interval [CI], 2.6 to 23.6), older age (OR, 2.2 per 10-year increment; 95% CI, 1.7 to 2.8), larger nodule diameter (OR, 1.1 per 1-mm increment; 95% CI, 1.1 to 1.2), and time since quitting smoking (OR, 0.6 per 10-year increment; 95% CI, 0.5 to 0.7). Model accuracy was very good (area under the curve of the receiver operating characteristic, 0.79; 95% CI, 0.74 to 0.84), and there was excellent agreement between the predicted probability and the observed frequency of malignant SPNs.

Conclusions—Our prediction rule can be used to estimate the pretest probability of malignancy in patients with SPNs, and thereby facilitate clinical decision making when selecting and interpreting the results of diagnostic tests such as PET imaging.

Keywords

coin lesion; diagnosis; lung neoplasms; pulmonary; receiver operating characteristic curve; statistical models; veterans

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The solitary pulmonary nodule (SPN) is an extremely common problem. An important early step in the management of patients with lung nodules is to estimate the clinical pretest probability of malignancy. Intuitively, management should be more aggressive when pretest probability is high and more conservative when pretest probability is low. While most clinicians use clinical experience and judgment to estimate pretest probability, some rely on one or more quantitative models that have been developed.¹⁻³ This information can be used to guide the selection and interpretation of subsequent diagnostic tests such as ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging and needle biopsy.

One widely cited prediction model for patients with SPNs was developed by investigators at the Mayo Clinic, who retrospectively reviewed the medical records and imaging tests of 419 patients with lung nodules that were newly discovered between 1984 and 1986.² The investigators identified the following six independent predictors of malignancy: older age; a history of smoking; a history of an extrathoracic cancer at least 5 years prior to the time of nodule detection; larger nodule diameter; upper lobe location; and the presence of spiculation. The accuracy of the model was good, with a mean ($\pm$ SD) area under the curve (AUC) of the receiver operating characteristic (ROC) of 0.83 ± 0.02 . Recently, the model was found to have similar accuracy (AUC, 0.79) in a retrospective cohort study⁴ of 106 patients with indeterminate lung nodules who were evaluated at a single center in the Netherlands, but the model tended to underestimate the probability of malignancy, especially in the lower range of predicted probabilities.

The Mayo clinic model has other limitations. It was developed in a cohort of patients with lung nodules who were originally managed > 20 years ago at a single tertiary care center in the midwestern United States. The investigators excluded patients with a history of lung cancer or a history of extrathoracic cancer within 5 years, further limiting the generalizability of the model. Furthermore, the prevalence of malignancy was relatively low (23%), and 12% of the patients did not have a final diagnosis. We therefore used available data from a recently completed Department of Veterans Affairs (VA) Cooperative Study^{5,6} (CSP 027), “¹⁸F-Fluorodeoxy-glucose (FDG) Positron Emission Tomography (PET) Imaging in the Management of Patients With Solitary Pulmonary Nodules,” to develop a new model to estimate the pretest probability of malignancy in a geographically diverse sample of veterans with SPNs.

Materials and Methods

Study CSP 027 was a prospective study that compared the accuracy of CT and FDG-PET scanning for the diagnosis of SPNs in veterans with nodules that measured between 7 and 30 mm in diameter on chest radiographs. Study methods have been described elsewhere.⁵ All participants in CSP 027 provided informed consent, and the study protocol was approved by the institutional review board at all 10 study sites. To perform our analysis, we received a waiver of informed consent and approval from the Stanford University institutional review board to merge VA administrative data with deidentified data from CSP 027.

Participants

Between September 1988 and June 2001, the CSP 027 study enrolled 532 participants at 10 geographically diverse VA sites (Ann Arbor, MI; Atlanta, GA; Buffalo, NY; Durham, NC; Indianapolis, IN; Madison, WI; Palo Alto, CA; St. Louis, MO; Seattle, WA; and West Los Angeles, CA). The primary eligibility criteria for enrollment in CSP 027 was the presence of a single, new, untreated, round, or oval opacity that measured between 7 and 30 mm on chest radiographs. Exclusion criteria included age < 21 years, presence of pregnancy or lactation, weight >350 to 400 lbs, intercurrent pulmonary infection, thoracic surgery within

6 months, radiotherapy to the chest within 1 year, and life expectancy of < 1 year. For this analysis, we excluded 157 participants who did not have a qualifying CT scan or PET scan and/or did not have a definitive diagnosis of an SPN as malignant or benign established at the conclusion of the study. A definitive malignant diagnosis was established by pathologic examination of tissue obtained via surgery or biopsy of the nodule, a mediastinal lymph node, or an extrathoracic site of clinically suspected tumor metastasis. A definitive benign diagnosis was established when a specific benign etiology was confirmed pathologically, or when the SPN was found to have been clinically and radiographically stable for at least 2 years.

Variables

Study CSP 027 collected information about age, gender, nodule diameter, nodule location, and smoking behavior, including current smoking status, number of years of smoking, average number of packs per day smoked, and number of years since quitting smoking. Although CSP 027 did not collect information about spiculation or other morphologic characteristics of nodules, readers of chest radiographs were asked to provide a radiographic diagnosis on a 5-point Likert scale that ranged between “definitely benign” and “definitely malignant.” We therefore used a radiographic diagnosis of “definitely malignant” as a proxy for spiculation, because spiculated nodules are approximately five times more likely to be malignant than benign.^{3,6}

We sought additional information about a history of cancer from utilization of electronic VA databases. Participant identities were confirmed by comparing both medical record number and birth date. We identified recent (*ie*, within 5 years) diagnoses of lung cancer and extrathoracic cancer by reviewing inpatient and outpatient data files. Because of the limitations of the VA databases, we were not able to identify study participants who had cancer diagnosed > 5 years before nodule detection.

Statistical Analysis

We used available data from study CSP 027 and VA utilization files to develop and internally validate a model of pretest probability that might prove to be especially helpful in veterans and similar groups of older men with SPNs.⁷ We developed the model by using stepwise logistic regression with the final diagnosis as the dependent variable and the following independent variables: age; gender; smoking history (never vs ever); number of pack-years smoked; years since quitting smoking; history of lung cancer; history of extrathoracic malignancy; time since previous lung cancer was diagnosed; time since previous extrathoracic cancer was diagnosed; nodule size; upper lobe location; right lung location; and a chest radiograph diagnosis of “definitely malignant.” Using backward selection, we arrived at a final parsimonious model by eliminating variables that were not statistically significant at a level of 0.05. Results were similar when we used a more liberal *p* value of 0.10 as the criterion for removal. All clinically plausible interactions were tested, but none were statistically significant, so they were not included in the final model. We report odds ratios (ORs) and 95% confidence intervals (CIs) for statistically significant predictors.

We used the Hosmer-Lemeshow goodness-of-fit statistic ($p > 0.05$) to evaluate model fit.^{8,9} We used the final model to calculate the estimated probability of malignancy in each study participant. We then compared the predicted probability of malignancy with the final diagnosis and constructed a ROC curve. To describe the accuracy of the model for identifying malignancy in CSP 027 study participants, we report the AUC and its 95% CI.¹⁰ To calibrate the model, we divided the study cohort into quintiles according to the predicted

probability of malignancy, and then plotted the observed probability of malignancy for patients within each quintile of predicted probability.¹¹

We internally validated the model by using a resampling or cross-validation procedure, which enabled us to use the full data set for model development.¹² To do this, we divided the study population into 10 equal groups by sampling randomly without replacement. For each group, we generated the predicted probability of metastasis by using parameters that were estimated from a logistic regression model that used data from the other nine groups. These 10 logistic regressions had identical specification; each used 90% of the data. We then calculated the AUC for the probabilities generated by the cross-validation. To demonstrate the potential clinical utility of the model, we used the Bayes theorem to calculate selected posttest probabilities of malignancy following FDG-PET scanning as a function of pretest probability and FDG-PET scan results.¹³

Results

The characteristics of 375 participants with benign and malignant SPNs are described in Table 1. The mean age was 65.9 ± 10.7 years. The prevalence of malignant SPNs was 54%. Most participants were either current smokers ($n = 177$) or former smokers ($n = 177$). Individuals with malignant nodules were older, were more likely to be current smokers, were more likely to have ever smoked, and had more pack-years of smoking experience. Former smokers with benign SPNs had quit smoking for more years than former smokers with malignant SPNs. Participants with malignant nodules were more likely to have a recent diagnosis of lung cancer and were somewhat more likely to have a history of extrathoracic cancer, but this latter difference was not statistically significant. Malignant nodules were larger, more likely to be located in an upper lobe, and more often regarded as definitely malignant on chest radiographs.

We identified four independent predictors of malignancy by using multivariate logistic regression analysis (Table 2). All other potential predictors were not associated with malignancy, and therefore were not included in the final model. Current or former smokers were approximately eight times more likely than never-smokers to have malignant nodules (OR, 7.9; 95% CI, 2.6 to 23.6). The likelihood of malignancy increased more than twofold for every 10-year increase in age (OR, 2.2; 95% CI, 1.7 to 2.8), and the likelihood increased by approximately 10% for every 1-mm increase in nodule diameter (OR, 1.1; 95% CI, 1.1 to 1.2). Finally, the likelihood of malignancy was approximately 40% lower for every 10-year increase in the number of years since quitting smoking (OR, 0.6; 95% CI, 0.4 to 0.7).

The clinical prediction model is described by the following equations:

$$\text{Probability of malignant SPN} = e^X / (1 + e^X) \quad (1)$$

$$X = -8.404 + (2.061 \times \text{smoke}) + (0.779 \times \text{age } 10) + (0.112 \times \text{diameter}) - (0.567 \times \text{years quit } 10) \quad (2)$$

where e is the base of the natural logarithm, smoke is 1 if a current or former smoker (otherwise 0), age10 is age in years divided by 10, diameter is the largest diameter of the nodule in millimeters, and yearsquit10 is the number of years since quitting smoking divided by 10.

Goodness-of-fit testing with the likelihood ratio and Hosmer-Lemeshow tests revealed that the model accounted for the outcome better than chance alone ($p < 0.001$) and that the

predicted likelihood of the outcome was similar to the observed likelihood ($p = 0.61$). A correlation matrix of parameter estimates revealed little evidence of multicollinearity.

The accuracy of the model was very good with an AUC of the ROC curve of 0.79 (95% CI, 0.74 to 0.84). The predicted probabilities that we generated with the cross-validation procedure had a similar AUC (0.78; 95% CI, 0.73 to 0.83). Model calibration was excellent; for participants in each quintile of predicted probability, the observed frequency of malignant SPNs was similar to the predicted probability (Fig 1). For example, among the 75 participants in the fourth quintile, the predicted probability of malignancy ranged between 66% and 79%, and the observed frequency of malignant SPNs in these participants was 72%.

To estimate the posttest probability of malignancy following FDG-PET scanning, we assumed that this test has a sensitivity of 94% and a specificity of 83% for identifying a malignant SPN, as was shown in a metaanalysis.¹⁴ When FDG-PET scan results are negative and the pretest probability is relatively low (20%), the resulting posttest probability of malignancy is $< 2\%$. In contrast, when PET scan results are negative and the pretest probability is relatively high (65%), the calculated posttest probability is $> 10\%$.

Discussion

The management of patients with SPNs continues to be challenging.¹⁵ In the present study, we used available data from a recently completed VA Cooperative Study and VA administrative databases to develop and internally validate a new model to estimate pretest probability and thereby to facilitate the management of patients with SPNs. We identified four independent predictors of malignant SPN, including a positive smoking history, older age, larger nodule diameter, and shorter time since quitting smoking. Importantly, we developed a parsimonious clinical prediction equation that estimates patient-specific probabilities of malignant SPN with very good accuracy and excellent calibration.

Our model has an accuracy that is similar to that of the model developed by Swensen and colleagues² at the Mayo Clinic. Like this previous model, our model included a positive smoking history, older age, and larger nodule diameter as independent predictors of a malignant SPN. However, in our model, the adjusted OR for a positive smoking history was higher than it was in the Mayo Clinic model. Unlike the Mayo Clinic group,² we found that a shorter time since quitting smoking was another independent predictor of malignancy. Furthermore, after adjusting for other potential predictors, we did not confirm their finding that upper lobe nodules were more likely to be malignant. While the Mayo Clinic investigators excluded patients with any history of lung cancer or a history of an extrathoracic cancer within 5 years, perhaps because they assumed that these would be strong predictors of malignant SPNs, we found that recently diagnosed lung or extrathoracic cancer were not independent predictors of malignancy. Unfortunately, we were not able to evaluate two other variables (*ie*, spiculation and a remote history of extrathoracic cancer) that were included in the Mayo Clinic model, because study CSP 027 did not collect data about these variables. Because of this, we were not able to perform an external validation of the Mayo Clinic model, nor were we able to compare the accuracy of our model to that of the Mayo Clinic model in CSP 027 study participants.

We and others^{16,17} have shown that the effectiveness and cost-effectiveness of strategies for SPN management depend critically on the pretest probability of malignancy. For example, Cummings et al¹⁶ showed that the choice among surgery, needle biopsy, and watchful waiting was a “close call.” Surgery was slightly more effective when the probability of cancer was $> 68\%$, needle biopsy was preferred when the probability was 3 to 68%, and

watchful waiting was preferred when the probability was $< 3\%$.¹⁶ In previous work,¹⁷ we confirmed and extended these findings by showing that it is highly cost-effective to use PET imaging rather than needle biopsy when the probability of cancer falls between 20 and 69%.

Our model can be used to generate pretest probabilities of malignant SPNs, and such estimates can facilitate interpretation of the results of subsequent diagnostic test results. As we demonstrated in our calculations, when the pretest probability of malignancy is relatively low (20%) and FDG-PET scan results are negative, the resulting posttest probability is $< 2\%$ and a subsequent strategy of watchful waiting would probably be justified. However, when PET scan results are negative and the pretest probability is relatively high (65%), the calculated posttest probability is $> 10\%$ and needle biopsy or video-assisted thoracic surgery biopsy should still be considered. This example illustrates how our prediction equation can be used to facilitate clinical decision making about the selection and interpretation of tests for SPN management. The equation can also be incorporated into a formal decision analysis or a cost-effectiveness analysis.

Our study has several limitations. We examined a relatively small number of clinical predictors, and the CSP 027 study collected little or no information about nodule morphology on chest radiograph or CT scan. Consequently, the model explained just $> 30\%$ of the variance in etiology, suggesting that additional predictors of malignant SPN remain unidentified. Because it was developed in a geographically diverse group of primarily older, white men with SPNs, our model may be particularly well suited for use in this patient population. However, the applicability of the model to women with solitary nodules is not known. In addition, the model is not suitable for use in patients with nodules that measure < 7 mm in diameter. Because the accuracy of the model likely depends on the prevalence of malignancy in the target population, it may not be well calibrated for use in populations in which the prevalence of malignancy is much lower or higher than that in our study. However, we think that the prevalence of malignancy in our study population is fairly representative of other groups, because VA study CSP 027 strove to reduce selection bias by enrolling all patients with SPNs on a qualifying chest radiograph. Some previous studies of patients with SPN have enrolled more selected groups of patients based on CT scan results or only when they received surgical treatment, resulting in an artificially high prevalence of malignancy.

Although the accuracy of the model was very good, we emphasize that the model is not intended to be used as a stand-alone test, but rather as a tool to help guide the selection and the interpretation of subsequent diagnostic tests. While cross-validation of the model yielded a similar AUC, our results still require external validation in an independent cohort of patients with SPNs. Despite these limitations, we conclude that the pretest probability of malignancy can be estimated by using a parsimonious clinical prediction equation that has the potential to facilitate clinical decision making in the management of patients with SPNs. The risk of malignancy is highest in older patients who are current smokers or recent quitters with larger SPNs.

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Abbreviations

AUC	area under the curve
CI	confidence interval
FDG	¹⁸ F-fluorodeoxyglucose
OR	odds ratio
PET	positron emission tomography
ROC	receiver operating characteristic

SPN solitary pulmonary nodule
VA Department of Veterans Affairs

Figure 1. Calibration curve for the clinical prediction model. The figure plots the observed frequency of malignancy as a function of the predicted probability of malignancy for patients in each quintile of predicted probability. The curve shows that the observed frequency of malignancy was similar to the predicted probability of malignancy for patients in each quintile. The range of predicted probabilities for patients in the first, second, third, fourth and fifth quintiles were < 0.29, 0.29 to 0.48, 0.48 to 0.66, 0.66 to 0.79, and > 0.79, respectively.

Table 1

Characteristics of Participants With Benign and Malignant SPNs*

Characteristics	SPN Groups		p Value
	Benign (n = 171)	Malignant (n = 204)	
Clinical			
Age, yr	62	68	< 0.0001
Male gender, %	97	98.5	0.33
Current smoker, %	40	53	0.02
Former or current smoker, %	91	97	0.01
Smoking history, pack-yr	46	63	< 0.0001
Time since quitting smoking, yr	8.1	5.6	0.03
History of other cancer, %	14	20	0.12
History of lung cancer, %	9	16	0.04
Radiologic			
Nodule size, mm	14.8	18.9	< 0.0001
CXR “definitely malignant,” %	1	4	0.09
Nodule location, %			
Upper lobe	46	54	0.11
Right lung	59	55	0.42
Time since diagnosis of lung cancer, d	316	368	0.67
Time since diagnosis of other cancer, d	460	620	0.11

* Values are given as the mean, unless otherwise indicated.

CXR = chest radiograph.

Table 2

Predictors of Malignant SPNs

Predictors	OR	95% CI
Smoking history*	7.9	2.6–23.6
Age per 10-yr increment	2.2	1.7–2.8
Nodule diameter per 1-mm increment	1.1	1.1–1.2
Time since quitting smoking per 10-yr increment	0.6	0.4–0.7

* Ever vs never.