The Lung Cancer Prediction Model "Stress Test":

Assessment of Models' Performance in a High-Risk Prospective Pulmonary Nodule Cohort

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Abstract

BACKGROUND: Pulmonary nodules represent a growing health care burden because of delayed diagnosis of malignant lesions and overtesting for benign processes. Clinical prediction models were developed to inform physician assessment of pretest probability of nodule malignancy but have not been validated in a high-risk cohort of nodules for which biopsy was ultimately performed.

RESEARCH QUESTION: Do guideline-recommended prediction models sufficiently discriminate between benign and malignant nodules when applied to cases referred for biopsy by navigational bronchoscopy?

STUDY DESIGN AND METHODS: We assembled a prospective cohort of 322 indeterminate pulmonary nodules in 282 patients referred to a tertiary medical center for diagnostic navigational bronchoscopy between 2017 and 2019. We calculated the probability of malignancy for each nodule using the Brock model, Mayo Clinic model, and Veterans Affairs (VA) model. On a subset of 168 patients who also had PET-CT scans before biopsy, we also calculated the probability of malignancy using the Herder model. The performance of the models was evaluated by calculating the area under the receiver operating characteristic curves (AUCs) for each model.

RESULTS: The study cohort contained 185 malignant and 137 benign nodules (57% prevalence of malignancy). The malignant and benign cohorts were similar in terms of size, with a median longest diameter for benign and malignant nodules of 15 and 16 mm, respectively. The Brock model, Mayo Clinic model, and VA model showed similar performance in the entire cohort (Brock AUC, 0.70; 95% CI, 0.64–0.76; Mayo Clinic AUC, 0.70; 95% CI, 0.64–0.76; VA AUC, 0.67; 95% CI, 0.62–0.74). For 168 nodules with available PET-CT scans, the Herder model had an AUC of 0.77 (95% CI, 0.68–0.85).

INTERPRETATION: Currently available clinical models provide insufficient discrimination between benign and malignant nodules in the common clinical scenario in which a patient is being referred for biopsy, especially when PET-CT scan information is not available.

Keywords

indeterminate pulmonary nodule; lung cancer; navigational bronchoscopy; prediction models; risk assessment

Pulmonary nodules are a significant health care concern, with an estimated 1.6 million new pulmonary nodules detected annually in the United States.[1] Early identification of malignant nodules is crucial to improve outcomes and expedite treatment of lung cancer. Lung cancer remains the leading cause of cancer-related mortality in the United States, with > 130,000 deaths annually and better outcomes associated with diagnosis at earlier stages.[2–4] However, distinguishing benign from malignant lung nodules for the purpose of determining who would most benefit from invasive diagnostic testing remains challenging. A cost-analysis demonstrated that up to 40% of the total cost of lung cancer workup is attributed to biopsies on benign lesions.[5]

Current guidelines recommend estimating the pretest probability of malignancy for pulmonary nodules to inform next steps in patient management, which ranges from conservative measures (eg, imaging surveillance) to invasive diagnostic testing or surgical resection. Both the American College of Chest Physicians and British Thoracic Society suggest the use of clinical prediction models to assist in estimating the pretest probability of malignancy to help guide next steps.[6,7] These models use clinical, demographic, and radiologic features to derive the probability of malignancy for a given nodule. Four commonly used prediction models recommended by society guidelines are the Brock, Mayo Clinic, Herder, and Veterans Affairs (VA) models. Training data sets on which these models were developed vary substantially in terms of cohort size, type of included or excluded nodules or patients, and prevalence of lung cancer. The models themselves differ in the number and type of variables included. The performance of these models has been evaluated retrospectively on several independent cohorts with area under the receiver operating characteristic curves (AUCs) reported around 0.90 but with notable variability.[8–11]

The utility of these models remains unknown in patients referred for consideration of biopsy of an indeterminate nodule. This population often has a high prevalence of malignancy which may affect the performance of certain clinical models developed on cohorts with lower malignancy prevalence. Additionally, individual patient risk factors which increase the physicians' concern for cancer warranting biopsy might not be accounted for in the discrete variables used as input for the aforementioned clinical risk models. Models with high performance and calibration in this clinical setting, however, would be useful and may reduce the number of unnecessary invasive biopsies while also allowing for timely diagnosis of lung cancer. In practice, these models are not often used for patients already being considered for biopsy. In this study, we chose to determine and compare the performance of four lung cancer prediction models on a high-risk nodule population referred for diagnostic navigational bronchoscopy. We hypothesized that models developed and calibrated on populations with characteristics (eg, lung cancer prevalence) more similar to the nodule cohort in this study would have better performance in this population than those that do not.

Study Design and Methods

Lung Nodule Cases

Consecutive patients with pulmonary nodules and masses referred to interventional pulmonology for navigational biopsy between November 7, 2017, and April 29, 2019, at a tertiary medical center were included in a prospective registry (Vanderbilt University Medical Center, institutional review board study No. 140274). All included cases underwent biopsy via navigational bronchoscopy. Of note, patients with multiple biopsied nodules or masses were included as unique cases. Any lung nodule or mass lost to follow-up before a final diagnosis was made or before the end of a 2-year surveillance period was excluded. Subsequently, masses (lesions < 30 mm in diameter) or secondary (metastatic) malignant lesions that were not of primary lung origin were excluded from the final nodule cohort. Expert lung pathologists' review of bronchoscopic and/or surgical histopathologic specimens consistent with either primary lung or metastatic malignancy was used for the adjudication of malignant diagnoses. Adjudication of benign diagnoses was based on the presence of specific benign histopathologic and/or microbiological findings that clearly explained the presence of the nodule (ie, granulomas, frank purulence, positive culture) or absence of growth after 2 years of follow-up for any nodules with nonspecific pathologic findings.

Variables

Clinical and demographic variables required to calculate lung cancer probability scores using the Brock, Mayo Clinic, and Herder models were prospectively collected from consultation, procedure, and progress notes in the electronic health record for each nodule case included in the cohort. Variables included age, sex, BMI, smoking history, history of extrathoracic and/or primary lung cancer, family history of lung cancer, history of COPD, symptoms prior to bronchoscopy, and FEV_1 % predicted on pulmonary function testing. Detailed smoking history included the general nature of smoking history (never, former, or current), pack-year history of smoking, and years since quitting for patients who previously smoked. Radiologic characteristics of each nodule were also extracted through visual assessment of the nodules within the health care system's shared imaging database by expert interventional pulmonologists and review of radiology reports available in the electronic health record. These variables included longest diameter, density, location by lobe, peripheral vs central location, presence of spiculation, and presence of emphysema. For patients who had serial scans including the nodule, it was noted if the nodule experienced any growth. In a subset of patients who also underwent PET-CT scan prior to biopsy, the degree of F-18 fluorodeoxyglucose avidity of the nodule was recorded using four categories (nonavid, faint, moderate, and intense).

Data Analysis

Imputation of missing data using the nearest neighbor methodology was performed for four patients who previously smoked with a missing years since quitting variable to allow for complete variable input for the VA model prior to analysis. Performance of the Brock (full model), Mayo Clinic, and VA models was subsequently evaluated on the study cohort by comparing predicted probabilities of malignancy to confirmed final

diagnoses and constructing receiver operator characteristic (ROC) plots. In a subset of patients who underwent a PET-CT scan, the performance of the Herder model was also evaluated by similarly comparing predicted probabilities of malignancy to confirmed final diagnoses and constructing an ROC plot. An agreement analysis was performed comparing the scores of the three models that do not require PET-CT input using Bland-Altman plots. Model calibration for the Brock, Mayo Clinic, and VA models was evaluated by generating calibration plots and calculating Brier scores for each model using 500 repetitions of bootstrap sampling. Model scores and population summary statistics were calculated in Microsoft Excel (Microsoft Inc). ROC plots were generated using GraphPad Prism (GraphPad). Calibration and agreement analyses were performed in R studio version 4.2 (R Core Team 2022) and the packages tidyverse and probably.

Results

Patient Cohort Characteristics

A total of 461 consecutively biopsied pulmonary nodules and masses in 393 patients were considered for analysis. Eleven pulmonary nodules in six patients were lost to follow-up and excluded from analysis. One hundred twenty-eight pulmonary nodules or masses in 105 patients were then excluded for having a diameter > 30 mm and final diagnosis being malignant not of primary lung origin. Therefore, the full cohort for primary analysis comprised 322 nodules in 282 patients. Only 5% of the nodules were detected on screening CT scans, whereas 95% of the nodules in this cohort were incidentally detected or detected on cancer surveillance imaging. The primary purpose for performing bronchoscopy in 313 out of 322 cases was for initial diagnosis (97% of the entire cohort), whereas only nine cases (3% of the entire cohort) underwent bronchoscopy for tissue acquisition and confirmation of a diagnosis. A final malignant diagnosis was determined for 185 nodules (57% of the study cohort). A final benign diagnosis was determined for 137 nodules (43% of the entire cohort), of which 65 (47% of benign nodules) lacked specific histopathologic or microbiological findings explaining the presence of the nodule but remained stable or regressed on surveillance imaging. Table 1 compares the clinical and radiologic characteristics of the malignant and benign nodule cohorts. Both cohorts were similar in terms of nodule size and density. Of note, the median nodule diameter for the malignant and benign cohorts was 16 and 15 mm, respectively. There were also similarities between the groups with respect to family history of lung cancer and percentage of patients with active tobacco use or patients who previously smoked. Malignant nodules were associated with older age, longer smoking exposure by pack-year history, prior history of cancer, and documented history of COPD. There was more evidence of emphysema, spiculation, and growth seen in malignant nodules than benign nodules. Tables 2 and 3 summarize the specific diagnoses for malignant and benign nodules, respectively. There were 168 nodules that also underwent PET-CT scans before bronchoscopy. In this subset, 130 nodules (77%) were malignant. Malignant nodules in this subset were more likely to have higher F-18 fluorodeoxyglucose avidity than benign nodules; however, missing PET-CT data were more common in the benign cohort (72% missing) vs the malignant cohort (30% missing).

Validation of the Brock, Mayo Clinic, VA, and Herder Models

In the full cohort analysis (N = 322), the AUCs for the Brock, Mayo Clinic, and VA models were 0.70 (95% CI, 0.64–0.76), 0.70 (95% CI, 0.64–0.76), and 0.67 (95% CI, 0.62–0.74), respectively. There were 168 nodules with associated PET-CT scans, and the Herder model AUC for this smaller subset was 0.77 (95% CI, 0.68–0.85). Figure 1 shows the ROC curves for the validation of the four models.

We assessed the performance of the individual models at prespecified thresholds for nodule risk categorization based on the American College of Chest Physicians 2013 guidelines[6] for the management of pulmonary nodules. At a risk threshold of 5%, the negative predictive value was 64% for the Brock model, 71% for the Mayo Clinic model, and 63% for the VA model. At the risk threshold of 65%, the positive predictive value was 83% for the Brock model, 73% for the Mayo Clinic model, and 75% for the VA model. Additionally, in this cohort, few nodules had an estimated probability of malignancy < 5% by American College of Chest Physicians guidelines. Less than 6% of the entire cohort was predicted to have a probability of malignancy of < 5% by the Brock, Mayo Clinic, or VA models. Conversely, less than one-third of the nodules had an estimated risk of malignancy of > 65% by the Brock, Mayo Clinic, or VA models. The Herder model categorized approximately 7% of nodules in the subset of nodules with available PET-CT scans as < 5% risk of malignancy with a negative predictive value of only 64%. The Herder model classified approximately 70% of the subset of nodules as > 65% risk of malignancy with a positive predictive value of 87%. An agreement analysis using Bland-Altman plots for the Brock, Mayo Clinic, and VA models (Fig 2) demonstrated low agreement among one another, especially for nodules with estimated probabilities falling within the intermediate range.

In a calibration analysis assessing models with complete data for the entire cohort, the Brier scores for the Brock, Mayo Clinic, and VA models were 0.28 (95% CI, 0.26–0.31), 0.23 (95% CI, 0.21–0.26), and 0.25 (95% CI, 0.22–0.27). Figure 3 shows the calibration plots for the three models for the entire cohort with the largest discrepancy in calibration for nodules with low-to-intermediate risk probabilities.

Discussion

In a cohort of indeterminate pulmonary nodules referred for biopsy via navigational bronchoscopy, commonly used risk assessment tools did not discriminate benign from malignant nodules. Our study highlights the need for risk models developed in and calibrated for clinical populations with intermediate-to-high prevalence of cancer.

Although the low negative predictive value of the models in this cohort is not surprising, we emphasize that well-calibrated models and biomarkers are currently needed for high-risk populations to better inform physician decision-making. Choi et al[12] articulate the importance of applying the appropriate lung cancer risk prediction model to the target population based on similarities in the target and model training populations. Factors (eg, context within which a nodule was identified, cancer prevalence within a population) may impact the calibration of a model to a particular cohort. The Brock model was developed using a large Canadian screening population of > 7,000 patients with a 5.5% prevalence of

cancer, whereas the Mayo Clinic model was developed on a population of 419 incidentally detected nodules with a 23% prevalence of cancer.[13,14] The Herder model was developed on a smaller cohort of 106 patients with incidentally detected nodules that were also referred for a PET-CT scan with a higher prevalence of malignancy at 57%.[15] The VA model was developed using 375 solitary pulmonary nodules initially identified on chest radiograph, and the prevalence of malignancy in this cohort was also high at 54%.[16] More recently, a predictive model (the Thoracic Research Evaluation and Treatment model) was developed using higher-risk presurgical populations for the purpose of assisting physicians in reducing unnecessary operations for benign processes. The most recent version of the Thoracic Research Evaluation and Treatment model shows better performance than the Brock, Mayo, and Herder models in a high-risk population perhaps due to its incorporation of greater clinical and radiologic data available at the time of evaluation, but this model requires additional external validation before its broader application.[17,18]

We postulate that the studied risk prediction models were not well calibrated for the study cohort for several reasons. First, we observed similarities between the benign and malignant cohorts in terms of specific clinical or radiographic features (eg, nodule diameter), which is used as variable input for most or all studied models. Second, the studied models do not consider growth of a nodule over time, which is a major limitation in their ability to estimate risk of malignancy. Third, the differences in lung cancer prevalence in training sets for the studied risk prediction models vs this study cohort may have also played a role in the models' calibration to the higher-risk data set. This may be true for the Brock and Mayo Clinic models, but the VA and Herder models were developed in cohorts with a prevalence of cancer of 54% and 57%, respectively. Finally, it is likely that the Brock model, developed on a population of screen-detected nodules, is less generalizable to this largely incidental nodule population.

Our study has several strengths. First, the study cohort represents a clinically relevant population limited to higher-risk indeterminate pulmonary nodules subjected to invasive testing. The primary purpose of bronchoscopy was for diagnosis of an indeterminate pulmonary nodule in 97% of the included cases, making this an ideal cohort for studying the performance of risk models applied to a high-risk indeterminate nodule population. Data for all nodules in the cohort were prospectively collected, and the cohort had a high rate of completed follow-up through histopathologic diagnosis and/or 2 years of surveillance. Additionally, in the cohort, differences between the malignant and benign cohorts were not confounded by size discrepancies, important limitations of prior retrospective validation studies.[19,20] The cohort in our study also included patients from a region with endemic fungi, an important contributor to benign lung nodules in midwestern and southeastern United States.

This study has several limitations. The study cohort includes patients with a history of intrathoracic or extrathoracic malignancies. Three of the prediction models (Brock, Mayo Clinic, and Herder models) were developed from cohorts that excluded most patients with recent lung or extrathoracic cancer. We chose to include these patients in our analysis for several reasons. First, there are differences in how each of these models excluded patients with prior malignancies. Second, the VA model development cohort included patients

with a prior history of cancer, and recently diagnosed lung or extrathoracic cancer was not found to be an independent predictor of malignancy during model development.[16] Third, an external validation study on 151 VA patients with nodules showed that the performance of the Mayo Clinic model was similar when patients with a prior history of lung cancer or recent extrathoracic malignancy were included compared with when they were excluded.[19] Given these prior findings and that patients with prior cancer history represent an important subset of referrals to navigational bronchoscopy, these patients were included in our analysis. We note that in selecting nodules for the study cohort, 128 out of 450 pulmonary lesions with known final diagnoses (28%) were excluded because of diameter > 3 cm or final diagnoses being malignancy not of primary lung origin. This highlights that a large proportion of patients in high-risk nodule clinics fall outside inclusion criteria for clinical risk models, limiting their generalizability to this population. Another limitation is that physician assessment of preprocedural probability of malignancy was not directly obtained for the nodules to compare the performance of physician assessment to the models' performance. However, we assumed the providers assessed the nodules in this cohort to have an intermediate-to-high preprocedural probability of malignancy given that all nodules underwent invasive diagnostic testing for the nodule of interest. The cohort in our study does not include indeterminate pulmonary nodules referred to CT-guided biopsy. We recognize that our findings may not be as generalizable to indeterminate pulmonary nodules referred for CT-guided biopsy for the initial diagnostic approach.

Interpretation

Commonly used pulmonary nodule risk assessment calculators do not discriminate benign lesions in patients referred for diagnostic biopsy by navigational bronchoscopy. To further reduce invasive biopsies for benign lesions, there is a need for more focused risk assessment tools. In this external validation study using a prospective population of patients with nodules referred for navigational bronchoscopy at a tertiary medical center, we observed that the Brock, Mayo Clinic, and VA models had fair discrimination of malignant and benign nodules, whereas the Herder model had higher performance when applied to the subset of nodules that had PET-CT scans prior to biopsy. However, very few patients were classified as low risk by any model to justify their use in assisting physician decision-making for deferring diagnostic biopsy. Our findings encourage the development of lung cancer prediction models and biomarkers trained and calibrated on high-risk nodule populations to augment physician assessment of indeterminate pulmonary nodules prior to invasive testing.

Funding/Support

Role of sponsors:

The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

ABBREVIATIONS:

AUC	area under the receiver operating characteristic curve
ROC	receiver operating characteristic
VA	Veterans Affairs

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Take-home Points

Study Question:

In this study, we evaluated and compared the performance of several clinical lung cancer prediction models in a high-risk population of pulmonary nodules referred for biopsy by navigational bronchoscopy.

Results:

The Herder model had the best performance on a subset of patients from this cohort, but all models demonstrated only modest performance with very few benign nodules being triaged to a low-risk category.

Interpretation:

This study highlights the need for the development and calibration of predictive models and biomarkers tailored to high-risk lung nodule populations.
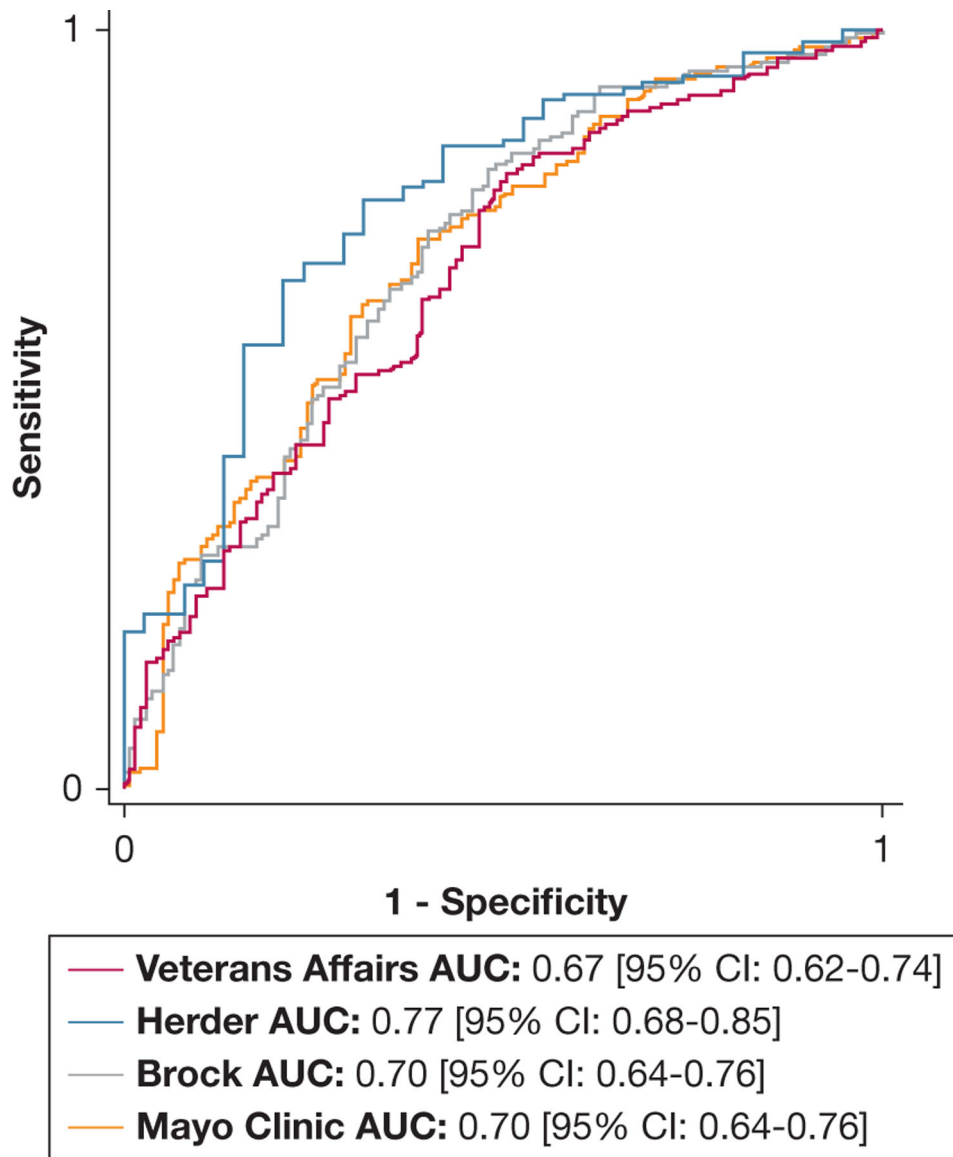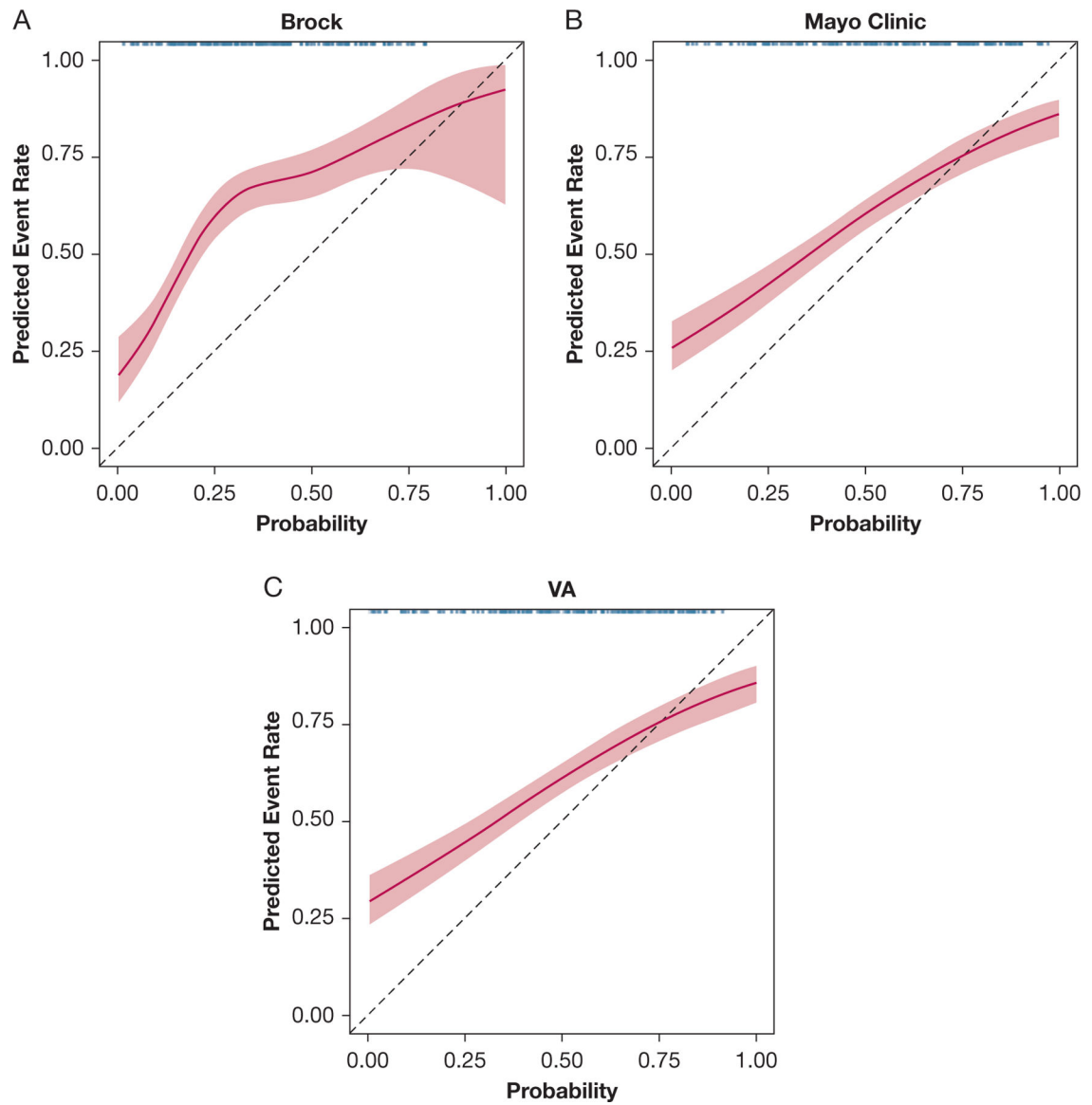
Figure 1 –.
Receiver operator characteristic curves for the entire nodule cohort (N = 322).[a] AUC = area under the receiver operating characteristic curve.

[a]Herder model was evaluated on a subset of nodules with available PET-CT scans (n = 168).
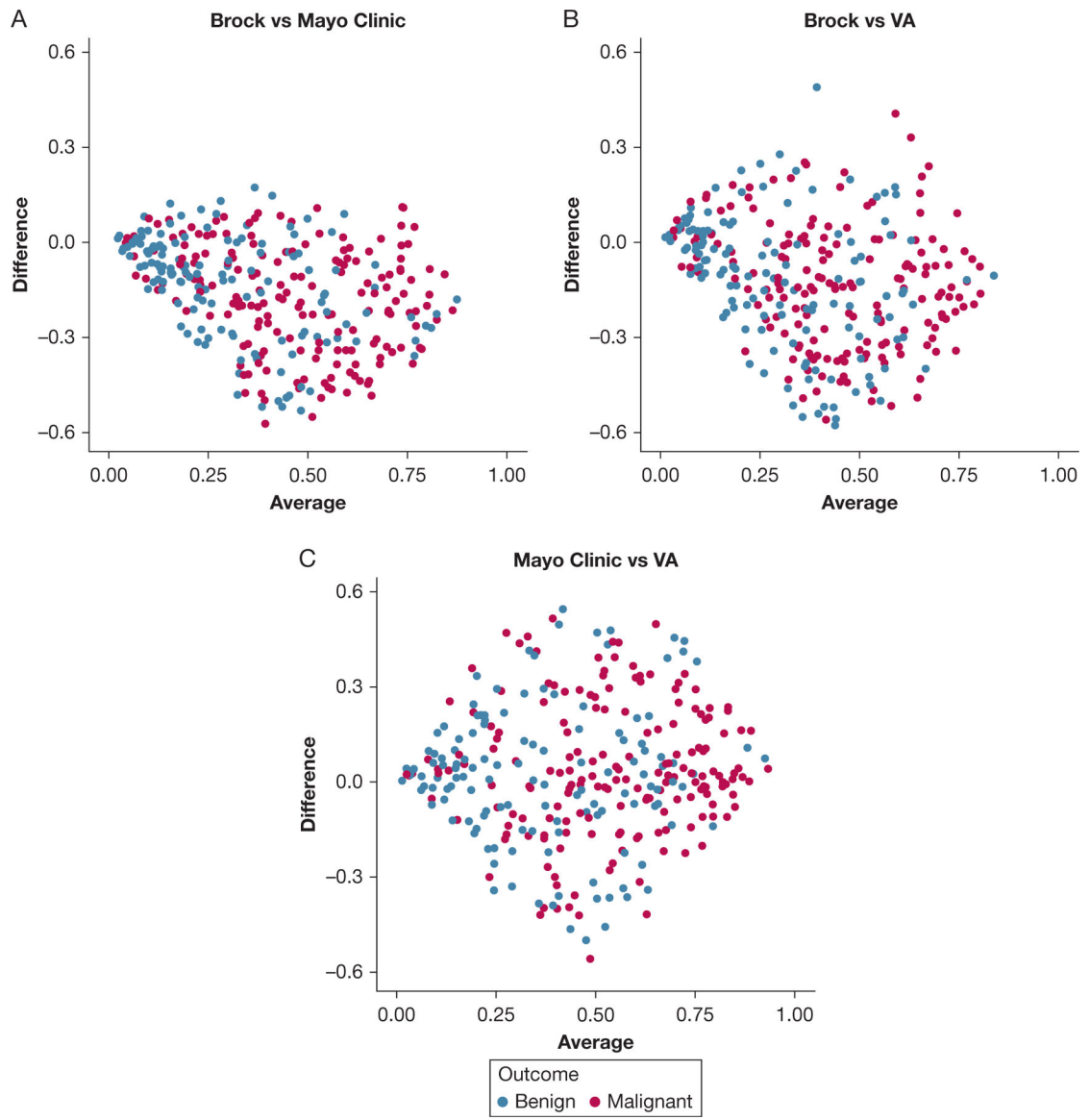
Figure 2 –.
A-C, Bland-Altman plots comparing Brock and Mayo Clinic model scores (A), Brock and VA model scores (B), and Mayo Clinic and VA model scores (C) (N = 322). Blue and red points represent benign and malignant nodules, respectively.

Figure 3 –.

A-C, Calibration plots for the Brock (A), Mayo Clinic (B), and VA (C) models on the entire cohort (N = 322).

TABLE 1

Comparison of Clinical and Radiologic Characteristics of Malignant and Benign Nodules (N = 322)

Variable	Malignant (n = 185)	Benign (n = 137)
Age, y	68 (61–73)	62 (53–71)
Biological sex, female	112 (61)	80 (58)
BMI, kg/m^2	26.2 (22.8–30.7)	26.5 (22.9–32.2)
Patient with active tobacco use or patient who previously smoked	152 (82)	93 (68)
Pack-y history of smoking[a]	33 (10–54)	10 (0–29.5)
Y since quiting smoking[b]	2.5 (0–13.3)	3 (0–21.5)
History of extrathoracic cancer	69 (37)	48 (35)
History of primary lung cancer	55 (30)	18 (13)
History of COPD	92 (50)	30 (22)
Symptomatic prior to bronchoscopy[c]	28 (15)	26 (19)
FEV$_1$ % predicted[d]	71 (54.5–87.5)	85 (68.5–96.5)
Family history of lung cancer	49 (27)	23 (17)
Longest diameter, mm	16 (13–21)	15 (11–21)
Location in upper lobes	122 (66)	63 (46)
Outer one-third of lung	125 (68)	93 (68)
Radiologic emphysema	101 (55)	35 (26)
Spiculation	110 (65)	40 (40)
Growth of nodule[e]	113 (61)	51 (37)
Density		
Solid	148 (80)	107 (78)
Part solid	31 (17)	25 (18)
Ground glass opacity	6 (3)	5 (4)
Nodule F-18 fluorodeoxyglucose avidity[f]		
Intense	89 (48)	16 (12)
Moderate	15 (8)	2 (2)
Faint	19 (10)	12 (9)
Nonavid	7 (4)	8 (6)

Variable	Malignant (n = 185)	Benign (n = 137)
No PET scan data	55 (30)	99 (72)

Values are median (interquartile range) or No. (%).

[a] Three nodules (0.9%) missing data.

[b] Four nodules (2.2%) missing data.

[c] One nodule (0.3%) missing data.

[d] One hundred thirty-four nodules (39%) missing data.

[e] One hundred twenty-seven nodules (39%) with no/insufficient serial imaging of specified nodule.

[f] One hundred fifty-four nodules (48%) missing data.

TABLE 2]

Specific Histopathologic Diagnoses for Malignant Nodules (n = 185)

Histopathology	No.	%
Primary lung cancer		
NSCLC		
Adenocarcinoma	109	92.4
Squamous cell	32	
NSCLC, not otherwise specified	21	
Clinical diagnosis (atypia/miss)	6	
Poorly differentiated carcinoma	2	
NSCLC with spindle features	1	
Small cell lung cancer	8	4.3
Carcinoid tumor	6	3.2

NSCLC = non-small cell lung cancer.

TABLE 3]

Specific Histopathologic Diagnoses for Benign Nodules (n = 137)

Histopathology	No.	%
Nonspecific/miss	65	47.4
Granulomatous	27	19.7
Purulent	10	7.3
Organizing pneumonia	11	8.0
Inflammation, atypical pathogen	9	6.6
Fibrosis/fibroelastotic scar	5	3.6
Hamartoma	3	2.2
Necroinflammatory	2	1.5
Inflammation, bacterial pathogen	2	1.5
Radiation fibrosis	1	0.7
Respiratory bronchiolitis	1	0.7
Lipoid pneumonia	1	0.7