Research Article

The Clinical Lung Cancer (ISSN 3064-6693)

Predictive Capacity For Malignancy Of The Scales For Evaluation Of Pulmonary Nodules In Oncological Patients At The National Institute Of Cancerology Between 2012 – 2022.

Luis Eduardo Ramírez Bejarano, María del Mar Meza Cabrera, Ana Milena Callejas, Carlos Andrés Carvajal, Edgar Alberto Sánchez Morales, Alfredo Saavedra Rodríguez.

Luis Eduardo Ramírez Bejarano: Department of Pulmonology. San José University Hospital. Colombia. Popayán.
Correo electrónico: luramirezb@unal.edu.co
ORCID: 0000-0002-5945-5419
María del Mar Meza Cabrera: Department of chest surgery. Western Clinic. Colombia. Cali.
Correo electrónico: mariadelmar1020@gmail.com
ORCID: 0000-0001-8273-6529
Ana Milena Callejas: Department of Pulmonology. National Cancer Institute. Colombia. Bogota.
Correo electrónico: amcallejasg@unal.edu.co
ORCID: 0000-0001-7917-0616
Carlos Andrés Carvajal: Department of chest surgery. National Cancer Institute. Colombia. Bogota.
Correo electrónico: ccarvajalmd@gmail.com
ORCID: 0000-0001-5915-0052
Edgar Alberto Sánchez Morales: Department of Pulmonology. National University Hospital of Colombia
Correo electrónico: easanchezm@unal.edu.co
ORCID: 0000-0002-5518-8149
Alfredo Saavedra Rodríguez: Department of Pulmonology. National Cancer Institute. Colombia. Bogota.
Correo electrónico: asaavedrar@unal.edu.co
ORCID: 0000-0002-4292-803X

***Corresponding author**

Dr.Luis Eduardo Ramirez Bejarano ,
Department of Pulmonology. San José University Hospital. Colombia. Popayán.
E-mail : lramirezb@hotmail.com

Received Date : October 30, 2024
Accepted Date : October 31, 2024
Published Date : November 29, 2024

ABSTRACT

Introduction: Pulmonary nodules are a common finding in chest imaging; their evaluation rules out malignant etiology to determine further management, which may include clinical follow-up, imaging studies, or biopsy. There are multiple scales to predict malignancy, most of which were developed in patients with incidental pulmonary nodules without a cancer history, so their application in such patients has not been discussed. The objective was to evaluate 5 malignancy prediction scales in patients with a cancer history.
Materials and Methods: A cross-sectional analytical study of diagnostic tests was conducted. Data were collected retrospectively from all patients with a cancer history who underwent resection of one or more pulmonary nodules between 2012 and 2022 at the National Institute of Cancerology. Clinical history data were collected and entered into the RedCAP platform, with data reviewed by the National Institute of Cancerology's defined oversight. Statistical analyses were performed using R software.
Results: Of the 180 patients included in the study, 61.1% were women, the average age was 56 years, and the most frequent cancer history was soft tissue sarcoma, accounting for 34.4%. In terms of etiology, 123 were malignant (68.4%), with the most common histopathological finding being metastases (57%) and 11.1% being primary lung adenocarcinoma.
Conclusion: Logistic regression analysis for calculating adjusted and unadjusted odds ratios demonstrated that the Bayesian model had the best performance in ruling out malignancy with a negative likelihood ratio (LR-) of 0.18 (p = 0.025). The nodule characteristics most correlated with malignancy were a size greater than 8 mm (OR 2.64) and the presence of more than 2 nodules (OR 2.191).

Keywords : Subsolid nodule, ground-glass nodule, mixed nodule, lung cancer, pulmonary nodule, smoking.

INTRODUCTION

Pulmonary nodules represent a clinical challenge due to the potential for either benign or malignant etiology. In 2015, in the United States, 80-90% of patients with malignant pulmonary

The Clinical Lung Cancer (ISSN 3064-6693)

nodules were diagnosed with lung cancer (1). The lungs are the second most common site for metastatic disease, encompassing all histological types (nearly 30% of cases) and are the sole site of metastasis in 20% of cases. Although most pulmonary metastases occur as multiple lesions, primary cancers that are more likely to present with single metastases include melanoma, sarcoma, and carcinomas of the colon, breast, kidney, and testis. When a pulmonary nodule is found in a patient with a known extrathoracic cancer, the likelihood of it being metastatic is approximately 25% (2).

The risk of malignancy in a pulmonary nodule can be assessed using prediction scales, which can guide subsequent management decisions, including clinical and imaging follow-up or biopsy/resection. The malignancy risk of a pulmonary nodule can be determined based on characteristics observed on chest computed tomography (CT), such as size, shape, margins, type (solid or subsolid), location, and growth rate, among others. These characteristics must be correlated with the clinical context of each patient (3).

There are multiple prediction scales for assessing the risk of malignancy in pulmonary nodules, but most validation studies have been conducted in patients with incidental pulmonary nodules who have no prior cancer history. Therefore, their application in patients with a cancer history is controversial (4). The most commonly used prediction scales are:

Cummings Model (Bayesian)

The variables in this scale include growth rate, location, margin type, nodule size, smoking history, history of malignancy, age, PET CT uptake, and density. The areas under the ROC curve for this model have been reported between 0.81 and 0.89 (5, 6).

Mayo Clinic Model

The variables in this scale include advanced age, smoking history, history of extrathoracic cancer at least 5 years prior to the nodule detection, larger nodule diameter, location in the upper lobe, and presence of spiculations. The areas under the ROC curve were 0.83 for the model development dataset and 0.80 for the validation dataset (7, 8). This is the model recommended by the CHETS 2013 guidelines for pulmonary nodule evaluation (41).

Herder Scale

This scale evaluated the value of adding the result of positron emission tomography with fluorodeoxyglucose (PET-FDG) to the Mayo Clinic model, achieving an area under the ROC curve of 0.92 (9, 10).

Brock Model

The variables in this scale include age, sex, family history of lung cancer, presence of emphysema, nodule size, nodule location in the upper lobe, nodule attenuation on computed tomography, nodule count, and presence of spiculation. The model demonstrated excellent discrimination, with an ROC greater than 0.90. In a screening setting, this model may be useful in deciding whether to continue with annual surveillance or pursue further investigation (6, 11).

Veterans Affairs Model

The VA model was developed using data from the Department of Veterans Affairs and a prospective study evaluating the accuracy of chest CT scans for diagnosing pulmonary nodules. It includes smoking history, advanced age, nodule diameter, and time since smoking cessation. An area under the ROC curve of 0.79 has been reported for this model (12, 13).

The use of the Brock, Herder, Mayo Clinic, Veterans Affairs, and Bayesian analysis models has been proposed to evaluate the pathological correlation of pulmonary nodules, although specific studies validating their use in patients with a history of cancer are lacking (4). Additionally, there is a lack of national data to determine which of these scales provides the best diagnostic performance for predicting the risk of malignancy in patients with pulmonary nodules and a history of cancer. Therefore, the objective of this study was to evaluate the predictive capacity for malignancy of five scales for the assessment of pulmonary nodules in oncological patients at the National Institute of Cancerology between 2012 and 2022.

METHODS

A cross-sectional, analytical diagnostic test study was conducted to compare the diagnostic performance of five scales against the gold standard (pathology results).

Information obtained from patient medical records was collected in a REDCAP database, and this data was reviewed by the institutional monitoring group to verify its accuracy.

Patients over the age of 18 who underwent resection of a single or multiple pulmonary nodules at the National Institute of Cancerology between January 2012 and December 2022 were included, provided they had a known oncological history and available pathology reports for the nodules. The nodule evaluated for assessment could have been singular; if multiple, the largest or dominant nodule was selected. Patients with inconclusive pathology reports for the resected pulmonary nodule were excluded. Demographic, clinical, and imaging variables were analyzed. Central tendency and dispersion measures were used for continuous variables, depending on data normality. Additionally, frequencies and percentages were used to describe categorical variables. The calculations for the five prediction scales (Bayesian, Mayo Clinic, Herder, Brock, and Veterans Affairs) for assessing nodule malignancy were performed. The results of the scales were categorized into two groups: the first as low malignancy risk with a percentage less than 5%, and the second group

The Clinical Lung Cancer (ISSN 3064-6693)

combining intermediate and high risks (5-65% and greater than 65%, respectively).

Logistic regression was performed to calculate crude and adjusted odds ratios (taking statistically significant variables into account) with a 95% confidence interval and a p-value <0.005. The scale calculations were made using validated web calculators. The software used for the analysis was R-Project v4.2.3.

The calculated sample size was 180 patients to achieve an 80% statistical power to detect a 0.05 difference between two diagnostic tests with sensitivities of 0.7 and 0.85. This was done using the PASS 2021® program.

The Research Ethics Committee of the National Institute of Cancerology approved the project protocol on February 15, 2023, according to Act No. 0003-23.

RESULTS

Data were collected from 180 patients who underwent surgical resection of pulmonary nodules at the National Institute of Cancerology from 2012 to 2022, all with a known oncological history. The average age of the patients was 56.7 years (Standard Deviation (SD) 13.9), and 110 (61.1%) of the patients were female. Of these patients, 67.8% were from Bogotá. The affiliation regime was similar across groups, with 45.6% being subsidized and 49.4% contributory. The average weight was 65.3 kg (SD 13.9), the average BMI was 26.14 kg/m² (SD 4.9), 22.8% of the patients were classified as obese, and 30.6% were classified as overweight (**Table 1**).

Table 1. Demographic and Anthropometric Characteristics

Variables	**Mean**	**Standard Deviation**	**Interquartile Range**
Age (years)	56.7	13.9	50 - 6
Gender		**n(%)**	
Female		110 (61.1)	
Male		70 (38.9)	
Origin		n(%)	
Bogotá		122 (67.8)	
Other		58 (32.2)	
Affiliation Regime		**n(%)**	
Subsidized		82 (45.6)	
Contributory		89 (49.4)	
Other		9 (5)	
Teaching		6	
Special		2	
Police affiliation		1	
Weight (kg)	65.32	13.91	55 – 71.75
Height (meters)	158	8.8	150 – 165
BMI (Body Mass Index)	26.14	4.99	22.5 – 29.5
		n(%)	
Underweight		6 (3.3)	
Normal weight		78 (43.3)	
Overweight		55 (30.6)	
Obesity Class 1		39 (21.7)	
Obesity Class 2		2 (1.1)	

The Clinical Lung Cancer (ISSN 3064-6693)

Regarding clinical characteristics, 14.4% of the patients had exposure to biomass for more than 10 years. 30.6% were exposed to tobacco smoking, of which 3.3% were active smokers and 26.6% were former smokers, with a median cessation time of 13 years (interquartile range of 7 – 22 years). The most common oncological history was soft tissue tumors at 34.4%, followed by gastrointestinal tumors at 21.7% and urological tumors at 15% (**Table 2**).

Table 2. Oncological History and Toxic Exposures.

Variables	n (%)	
COPD (Chronic Obstructive Pulmonary Disease		
Yes	5 (2.8)	
No	175 (97.2)	
Exposure to biomass for more than 10 years		
Yes	26 (14.4)	
No	144 (80)	
Unknown	10 (5.6)	
Active smoker		
Yes	6 (3.3)	
No	174 (96.7)	
Former smoker		
Yes	48 (26.7)	
No	132 (73.3)	
Years since smoking cessation	Median	Interquartile range
n = 48	13	7 – 22.5
Current/former smoker		
Yes	55 (30.6)	
No	125 (69.4)	
Pack-Year Index (PYI)	Median	Interquartile range
(IPA) n = 55	2	1-3
Extrathoracic cancer > 5 years		
Yes	52 (28.9)	
No	128 (71.1)	
Emphysema		
Yes	5 (2.8)	
No	175 (97.2)	
Family history of cancer		
Yes	55 (30.6)	
No	113 (62.8)	
Unknown	12 (6.7)	
Radiotherapy		
Yes	83 (46.1)	
No	97 (53.9)	
Oncological History		
Soft tissue	62 (34.4)	
Gastrointestinal	39 (21.7)	
Urological	27 (15)	
Gynecological	23 (12.8)	
Endocrinological	12 (6.7)	
Bone	9 (5)	
Hematological	5 (2.8)	
Pulmonary	2 (1.1)	
Nasopharyngeal	1 (0.6)	

The Clinical Lung Cancer (ISSN 3064-6693)

In terms of imaging characteristics, 78.9% of patients had nodules ≥ 8 mm, with 75% being solid, 47.8% having smooth margins, and 56.1% located in the lower lobes. 86.1% of patients did not undergo 18 FDG-PET-CT; of the 24 patients who did, 7.8% had an SUV < 2.5. Out of 180 patients, focal density could be assessed in 131, with 51.1% having a density > -30 HU. The nodule doubling time (VDT) could be evaluated in 56 patients, with 29.4% having an average range of 25 to 400 days. Other imaging and non-imaging variables assessed (nodule type, margins, location, calcification, VDT, density), as well as a family history of pulmonary cancer or extrathoracic cancer greater than 5 years, did not show statistical significance (**Table 3**).

Table 3. Clinical Characteristics of Patients by Histological Type.

Feature	Patients No. (%)		p-value
	Benign nodules (n = 58)	Malignant nodules (n = 122)	
nodule size			
≤ 8 mm	19 (32.8)	19 (15.6)	<0.01
> 8 mm	39 (67.2)	103 (84.4)	
Recuento de nódulos			
≤ 2	35 (60.3)	50 (41.0)	0.015
> 2	23 (39.7)	72 (59.0)	
nodule count			
Solid	41 (70.7)	94 (77.0)	0.546
Partially solid	15 (25.9)	26 (21.3)	
Ground-glass	2 (3.40)	2 (1.60)	
Nodule Margin			
Smooth	33 (56.9)	53 (43.4)	0.231
Lobulated	14 (24.1)	41 (33.6)	
Spiculated	11 (19.0)	28 (23.0)	
Nodule Location			
Lower lobes	33 (56.9)	68 (55.7)	0.862
Middle lobes	4 (6.90)	12 (9.80)	
Upper lobes	21 (36.2)	42 (34.4)	
Calcification			
Yes	4 (6.90)	1 (0.80)	0.038
No	54 (93.1)	121 (99.2)	
Doubling Time of Volume			
25 – 400 days	9 (15.5)	44 (36.1)	1
401 – 900 days	0 (0.00)	3 (2.50)	
Unknown	49 (84.5)	75 (61.5)	
Density			
<-60 HU	16 (27.6)	18 (14.8)	0.182
-60 to -30 HU	1 (1.70)	4 (3.30)	
-30 HU	27 (46.6)	65 (53.3)	
Unknown	14 (24.1)	35 (28.7)	
PET FDG			
SUV 2.5	3 (5.20)	11 (9.00)	1
SUV > 2.5	2 (3.40)	8 (6.60)	
Unknown	53 (91.4)	103 (84.4)	
Extrathoracic Cancer > 5 years			
Yes	15 (25.9)	37 (30.3)	0.417
No	43 (74.1)	85 (69.7)	

Source: Database

The Clinical Lung Cancer (ISSN 3064-6693)

Regarding the etiology of pulmonary nodules, 57 patients (31.6%) had a benign etiology, with anthracosis being the most common (29.8%); 123 patients (68.4%) had a malignant etiology, with metastases being the most frequent diagnosis at 57%, followed by lung adenocarcinoma (11.1%). Among the metastases, breast cancer was the most common, with 18 patients (14.6%) (**Table 4**).

Table 4. Biopsy Results of Pulmonary Nodules and Statistical Model Probabilities.

Variables	**n (%)**
Histology Type:	
Benign	57 (31.6)
Malignant	123 (68.3)
Benign:	
Anthracosis	17 (29.8)
Non-necrotizing granuloma	9 (15.8)
Necrotizing granuloma	8 (14)
Hamartoma	8 (14)
Caseating granuloma	5 (8.7)
Organized pneumonia	4 (7)
Hyalinized granuloma	2 (3.5)
Chronic inflammation	2 (3.5)
NINE (Neuroendocrine Neoplasm, Not Otherwise Specified)	1 (1.7)
Paraganglioma	1 (1.7)
Malignant:	
Lung adenocarcinoma	20 (11.1)
Metastasis	103 (57)
Breast cancer	18 (14.6)
Colon cancer	11 (8.9)
Kidney cancer	9 (7.3)
Rectal cancer	8 (6.5)
Sarcoma	8 (6.5)
Thyroid cancer	7 (5.7)
Melanoma	6 (4.8)
Neuroendocrine tumor	5 (4.1)
Cervical cancer	5 (4.1)
Endometrial cancer	4 (3.2)
Adenoid cystic carcinoma	3 (2.4)
Penile cancer	3 (2.4)
Bladder cancer	3 (2.4)
Chondrosarcoma	3 (2.4)
Gastric cancer	2 (1.6)
Ovarian cancer	2 (1.6)
Non-keratinizing squamous cell carcinoma	2 (1.6)
Pleomorphic adenoma	1 (0.8)
Adrenal cancer	1 (0.8)
Vaginal trophoblastic cancer	1 (0.8)
Bone giant cell tumor	1 (0.8)

The Clinical Lung Cancer (ISSN 3064-6693)

By employing a Bayesian Model, we successfully identified 98 out of every 100 patients with a history of cancer as diseased, highlighting its high sensitivity in detecting positive cases. However, there is a limitation in its ability to classify negatives, showing only a 14% accuracy in identifying individuals without malignant nodules. When this Bayesian Model is applied to assess patients with intermediate-high risk, it shows a substantial 70% probability that a positive result effectively indicates the presence of lung cancer, underscoring its usefulness in higher-risk situations. In cases where the model indicates low risk in patients with a history of cancer, the probability that the nodule is benign reaches 73%, demonstrating its ability to discern less concerning situations. Additionally, there is a 1.13-fold increased probability of having a malignant nodule when the Bayesian Model indicates intermediate-high risk. Conversely, the probability of a benign nodule increases significantly (5.5 times) when the Bayesian Model reports low risk (**Table 5**). Sensitivity 0.98, Specificity 0.14, Positive Predictive Value (PPV) 0.70, Negative Predictive Value (NPV) 0.73, Positive Likelihood Ratio (LR) 1.13, Negative LR 0.18.

Table 5. Sensitivity, Specificity

Scores	Sensitivity (IC95%)	Specificity (IC95%)	VPP (IC95%)	VPN (IC95%)	LR + (IC95%)	LR - (IC95%)
Bayesiano	0.98 (0.93-0.99)	0.14 (0.06-.025)	0.70 (0.63-0.77)	0.73 (0.39-0.94)	1.13 (1.02-1.26)	0.18 (0.05-0.65)
Herder	0.75 (0.66-0.82)	0.36 (0.24-0.50)	0.71 (0.62-0.73)	0.40 (0.27-0.55)	1.17 (0.94-1.46)	0.70 (0.44-1.11)
Mayo Clinic	0.75 (0.66-0.82)	0.36 (0.24-0.50)	0.71 (0.63-0.73)	0.40 (0.27-0.55)	1.17 (0.94-1.46)	0.70 (0.44-1.11)
VA	0.72 (0.63-0.80)	0.44 (0.32-0.58)	0.73 (0.64-0.81)	0.43 (0.31-0.57)	1.31 (1.01-1.69)	0.62 (0.42-0.93)
Brock	0.62 (0.53-0.71)	0.53 (0.40-0.67)	0.74 (0.64-0.82)	0.40 (0.29-0.52)	1.34 (0.98-1.82)	0.71 (0.51-0.98)

During the logistic regression analysis, it was observed that a Bayesian Model classified as intermediate-high has a fivefold higher probability of being malignant compared to other models, with this association being statistically significant ($p < 0.01$; 95% CI: 1.33 – 24.2) (**Table 6**).

Table 6. Results of Logistic Regression Adjustment for Each Risk Quantification Model (Intermediate and High Risk Grouped)

Feature	Unadjusted OR[IC95%]	p-value	Adjusted OR [IC95%]	p-value
VA model				
Low Intermediate & High	Ref. 2.10 [1.09 – 4.05]	0.025*	Ref. 1.65 [0.77 – 3.50]	0.190
Mayo clinic				
Low Intermediate & High	Ref. 1.66 [0.85 – 3.26]	0.137		
Brock				
Low Intermediate & High	Ref. 1.90 [1.01 – 3.59]	0.047*	Ref. 1.31 [0.62 – 2.73]	0.467
Herder				
Low Intermediate & High	Ref. 1.66 [0.85 – 3.26]	0.137		
Bayesiano				
Low Intermediate & High	Ref. 6.34 [1.75 – 29.9]	<0.01*	Ref. 5.02 [1.33 – 24.2]	0.024*

CI: Confidence Interval
OR: Odds Ratio
Source: Database

The Clinical Lung Cancer (ISSN 3064-6693)

After adjusting the model, it is observed that the presence of more than two nodules increases the probability of malignancy by 2.97 times (95% CI: 1.49-6.18), indicating a significant association with an increased likelihood of malignant cases. Similarly, the absence of calcification is notably associated with a 10.4-fold increase in the probability of malignancy (95% CI: 1.34-214), highlighting the importance of this factor as a significant predictor in identifying malignant cases (**Table 7**).

Table 7.

Feature	Unadjusted OR [IC95%]	p-value	Adjusted OR [IC95%]	p-value
Nodule size				
≤ 8	Ref.		Ref.	
> 8	2.64 [1.26 – 5.54]	<0.01	1.87 [0.81 – 4.28]	0.133
Number of Nodules				
≤ 2	Ref.		Ref.	
> 2	2.19 [1.16 – 4.19]	0.016	2.97 [1.49 – 6.18]	< 0.01
Calcification				
Yes	Ref.		Ref.	
No	8.96 [1.28 – 77.5]	0.052	10.4 [1.34 – 214.4]	0.046
Bayesian				
Low	Ref.		Ref.	
Intermediate & High	6.34 [1.75 – 29.9]	<0.01	7.96 [1.98 – 40.8]	<0.01

CI: Confidence Interval
OR: Odds Ratio
Source: Database

DISCUSSION

The approach to pulmonary nodules in cancer patients presents a challenge for specialties dealing with the management of these patients. To date, there are no available data in Colombia to determine the incidence and prevalence of pulmonary nodules in patients with or without a history of cancer. The etiology of pulmonary nodules is varied, making their diagnostic and therapeutic approach complex. In the general population, most pulmonary nodules are of benign etiology (18), while around 15 to 20% are malignant (19, 20, 42). Regarding imaging characteristics, pulmonary nodules can be classified as solid or subsolid. Subsolid nodules can be further divided into two categories: ground-glass opacities and partially solid nodules. In our study, 122 patients had malignant pathology, of which 77% were solid, 20.6% were partially solid, and 1.6% were ground-glass opacities (17, 21).

A direct relationship between nodule size and the likelihood of malignancy has been established; larger nodules have a higher risk of being malignant, although small nodules cannot be excluded from being malignant (22). In the general population, nodules with diameters less than 5 mm have a malignancy potential of 0-1%, those between 5 and 10 mm have a malignancy potential of 6%-28%, and those larger than 20 mm have a malignancy potential of 64%-82% (23, 24, 25). Our study is consistent with this finding, as having a nodule larger than 8 mm increases the probability of malignancy with statistical significance (OR 2.64, p < 0.01).

Additionally, having more than 2 pulmonary nodules (OR 2.19, p = 0.016) showed statistical significance in predicting malignancy, which aligns with findings presented in the manuscript by Petrella et al., where it is noted that multiple pulmonary nodules in a patient with a history of cancer suggest a metastatic component (43).

Regarding nodule margins, it has been determined that nodules with smooth margins are more likely to be benign, while those with spiculated, lobulated, or irregular margins are more suggestive of malignancy (26). Gurney et al. described that patients with a single pulmonary nodule with spiculated, lobulated, or irregular margins have a malignancy rate between 33% and 100%, with a positive predictive value of 90% (27). However, the presence of smooth margins does not rule out malignancy, as 10% of pulmonary metastases and nearly 20% of primary lung tumors present with smooth margins (28). In our study, nearly 50% of the included population had nodules with smooth margins, but we did not find a statistically significant association between this characteristic and its etiology (P = 0.231).

The Clinical Lung Cancer (ISSN 3064-6693)

An increase of 26% in the diameter of a pulmonary nodule corresponds to a doubling of its size. When this tumor doubling time (TDT) occurs between 30 and 400 days of follow-up, it is associated with malignant etiology. Nodules that double in size more rapidly or more slowly are generally benign (with a parameter time of 20 days). Nodule stability, defined as no growth over 2 years, is an indicator of benign cause (29). In our study, it was not possible to calculate the TDT for most nodules due to the absence of prior comparative imaging studies. However, among those patients for whom the TDT was calculated, 29.4% had a TDT of 25 to 400 days.

Regarding the location of nodules with malignant potential, they are generally found in the upper lobes, particularly in the right upper lobe (30). In our study, most resected nodules were located in the lower lobes, and no statistically significant association between location and malignancy was found (P =0.862). In patients with a history of cancer, determining the risk of developing new primary or secondary lung tumor pathology is of vital importance. The prevalence of pulmonary metastases is reported to be up to 54% (31). Therefore, finding a pulmonary nodule in a patient with a history of malignancy should be individualized based on risk to determine the best approach for follow-up and treatment. In our study, 57% of resected pulmonary nodules were of metastatic etiology, a value similar to that found in the literature, and 11.1% corresponded to primary lung neoplasms such as adenocarcinoma, a non-negligible percentage in a population with a cancer history. International reports document an incidence ranging between 0.8% and 17%.

The establishment of predictive models for malignancy is necessary in the diagnostic algorithm for decision-making. However, these models have several limitations due to the number of variables and characteristics included (32). Additionally, these models are applied to patients with solitary or multiple pulmonary nodules without a history of cancer, where their performance has not been studied.

When evaluating the results of the Bayesian model published in 2014, the variables with the best prediction of malignancy were size (>16 mm, LH+ 2.3), enhancement (>40 HU, LH+ 5.0), morphology (spiculated, LH+ 7.88), and volume doubling time (25-400 days, LH+ 14.4) (33). In comparison to our results, we did not find statistical significance for these variables except for nodule size (>8 mm, OR 2.64, $p < 0.01$), which is consistent with the literature in its association with malignancy. One limitation to consider was that 86.2% of patients did not undergo 18 FGD-PET-CT, 27% did not have nodule density calculated, and 68.9% did not have VDT calculated due to the absence of comparative images. Additionally, some radiology reports did not include nodule density values in Hounsfield units, and older studies lacked images in the system for review. However, this situation did not affect the applicability of the scales in the study, as the scoring calculation accommodates the absence of these data. When performing logistic regression, this model had the best performance with an adjusted OR of 5.02 and a statistically significant p-value of 0.024. The National Cancer Institute has had a PET CT service since 2012 (34). Unfortunately, due to high demand and prolonged wait times, it has not been a protocolized resource for studying pulmonary nodules in patients with a cancer history, a situation that is clearly evident in the results.

In the Brock model published in 2013, the variables predicting malignancy were advanced age (>65 years, OR 1.03), female gender (OR 1.82), family history of lung cancer (OR 1.34), emphysema (OR 1.34), size (14 mm), location (upper lobe, OR 1.93), partially solid nodule (OR 1.46), lower nodule count in patients with multiple pulmonary nodules (<4, OR 0.92), and spiculation (OR 2.17). One limitation mentioned in the study (McWilliams et al.) was inadequate applicability for screening low-risk populations and for patients with hilar or mediastinal lymphadenopathy (35); in our study, evaluating these variables did not show statistical significance.

In the Mayo Clinic model published in 1997, the variables predicting malignancy were age (>65 years, OR 1.01), smoking (OR 3.12), cancer diagnosis more than 5 years ago (OR 2.37), size (17 mm, OR 1.13), spiculation (OR 3.17), and upper lobe location (OR 1.81) (36). In the Herder model published in 2005, the FDG-PET variable was added, classifying results into 4 intensity categories, improving the probability of malignancy by 13.6% (37). In our study, we did not find statistical significance in the results of these two models, and as described above, this may be related to the lack of FDG-PET in a large number of patients (86.7%).

In the VA model published in 2007, variables predicting malignancy included smoking history (OR 7.9), advanced age (>65 years, OR 2.2), size (>7 mm, OR 1.1), and smoking cessation (less than 10 years, OR 0.6) (38). In our study, neither the scale nor the variables analyzed independently showed statistical significance. The average age in our study was 53 years, which may be related to the lack of association with malignancy. Analyzing the five models, advanced age (>65 years) was identified as a predictor of malignancy, a variable that did not show statistical significance in our study.

Our study showed that the Bayesian Model had a sensitivity of 98% and a specificity of 14%. When comparing these results with those reported by Zhang et al. (39), significant differences in sensitivity and specificity of other models are evident. In particular, for the Herder model, we observed a sensitivity of 93% and a specificity of 69%, surpassing Zhang et al.'s figures (75% and 36%). Likewise, the Mayo Clinic model showed a sensitivity of 68% and a specificity of 67%, contrasting with Zhang et al.'s values (75% and 36%). For the VA model, our research revealed a sensitivity of 62% and a specificity of 8%, diverging again from Zhang et al.'s results (72% and 44%). Despite the Bayesian Model's high sensitivity, its low

The Clinical Lung Cancer (ISSN 3064-6693)

specificity is noteworthy. This discrepancy may be attributed to the heterogeneity of the studied sample, suggesting the need for careful interpretation of results and highlighting the importance of considering specific population characteristics in the performance analysis of the models.

Additionally, it is important to highlight that the model adjusted through logistic regression reveals a significant and robust relationship between the intermediate-high categorization of the Bayesian Model and the probability of malignancy. These results reinforce the validity and utility of the Bayesian Model in identifying potentially higher-risk cases, providing a solid foundation for considering this approach in evaluating patients with a cancer history.

The IDEAL study (Artificial Intelligence and Big Data for Early Lung Cancer Diagnosis) uses a prediction model called "Lung Cancer Prediction CNN (LCP-CNN)" with an algorithm known as Convolutional Neural Networks (CNN). Initially applied to data from the US NLST (National Lung Screening Trial) under the supervision of expert thoracic radiologists to evaluate its performance in patients with pulmonary nodules who underwent the Brock score. The main result showed an area under the curve of 89.6% (95% CI 87.6–91.5) for the artificial intelligence model compared to 86.8% for the Brock score, with a significant difference ($p<0.005$) favoring the former. Additionally, there was one false negative case compared to six cases with the Brock model (40). These results conclude that the tool is promising in the study of pulmonary nodules, but it should be noted that incidental nodules were included and this tool was not validated in patients with a cancer history.

Among the study's limitations is its retrospective design. Retrospective data collection often risks missing information, which limits the total sample size of the study. Additionally, 18-FDG PET-CT was not requested in 86.2% of patients. Furthermore, density and VDT calculations were only performed for 131 patients due to the absence of images for older cases or the lack of comparative images (cases with only one CT scan used for the decision of surgical resection).

CONCLUSION

The literature is limited regarding studies that apply and evaluate the diagnostic value of probabilistic models for pulmonary nodule malignancy in patients with a history of cancer. Therefore, the results obtained in this research provide valuable insights into the behavior of pulmonary nodules in the local population with known oncological diagnoses. This study highlights four statistically significant parameters to consider when addressing a pulmonary nodule: the application of the Bayesian score, having more than two nodules, nodule size greater than 8 mm, and the absence of calcification.

This study paves the way for future research in the oncological population with pulmonary nodules to determine variables related to the probability of malignancy and to develop algorithms for diagnostic and therapeutic approaches at the National Cancer Institute.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015 Jan-Feb;65(1):5-29. doi: 10.3322/caac.21254. Epub 2015 Jan 5. PMID: 25559415. doi: 10.3322/caac.21254.

2. Callister MEJ, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, Franks K, Gleeson F, Graham R, Malhotra P, Prokop M, Rodger K, Subesinghe M, Waller D, Woolhouse I. British Thoracic Society guidelines for the investigation and management of pulmonary nodules: accredited by NICE. Thorax. 2015 Jun 16;70(Suppl 2). doi: 10.1136/thoraxjnl-2015-207168.

3. Horeweg N, van Rosmalen J, Heuvelmans MA, van der Aalst CM, Vliegenthart R, Scholten ET, ten Haaf K, Nackaerts K, Lammers JJ, Weenink C, Groen HJ, van Ooijen P, de Jong PA, de Bock GH, Mali W, de Koning HJ, Oudkerk M. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. Lancet Oncol. 2014 Nov;15(12):1332-1341. doi.org/10.1016/S1470-2045(14)70389-4

4. Choi HK, Ghobrial M, Mazzone PJ. Models to Estimate the Probability of Malignancy in Patients with Pulmonary Nodules. Annals ATS. Oct 2018;15(10):1117-26. doi: 10.1513/AnnalsATS.201803-173CME.

5. Gurney JW, Lyddon DM, McKay JA. Determining the likelihood of malignancy in solitary pulmonary nodules with Bayesian analysis. II. Application. Radiology. 1993;186(2):415-422. doi: 10.1148/radiology.186.2.8421744.

6. McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med. 2013;369:910-919. doi: 10.1056/NEJMoa1214726.

7. Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. Arch Intern Med. 1997 Apr 28;157(8):849-55. PMID: 9129544. doi.org/10.1001/archinte.157.8.849

8. Deppen SA, Blume JD, Aldrich MC, Fletcher SA, Massion PP, Walker RC, et al. Predicting lung cancer prior to surgical resection in patients with lung nodules. J Thorac Oncol. 2014;9:1477-1484. doi: 10.1097/JTO.0000000000000287.

9. Gould MK, Ananth L, Barnett PG; Veterans Affairs SNAP Cooperative Study Group. A clinical model to estimate the pretest probability of lung cancer in patients with solitary pulmonary nodules. Chest. 2007;131:383-388. doi: 10.1378/chest.06-1261.

10. Mosmann MP, Borba MA, Negromonte de Macedo FP, de Araujo Lima Liguori A, Villarim Neto A, de Lima KC. Solitary pulmonary nodule and 18F-FDG PET/CT. Part 2: accuracy, cost-effectiveness, and current recommendations. Radiol Bras. 2016;49:104-111. doi: 10.1590/0100-3984.2014.0012.

11. Al-Ameri A, Malhotra P, Thygesen H, Plant PK, Vaidyanathan S, Karthik S, et al. Risk of malignancy in pulmonary nodules: a validation study of four prediction models. Lung Cancer. 2015;89:27-30. doi: 10.1016/j.lungcan.2015.03.018.

12. Gould MK, Ananth L, Barnett PG; Veterans Affairs SNAP Cooperative Study Group. A clinical model to estimate the pretest probability of lung cancer in patients with solitary pulmonary nodules. Chest. 2007;131:383-388. doi: 10.1378/chest.06-1261.

13. Schultz EM, Sanders GD, Trotter PR, Patz EF Jr, Silvestri GA, Owens DK, et al. Validation of two models to estimate the probability of malignancy in patients with solitary pulmonary nodules. Thorax 2008;63:335–341. doi: 10.1136/thx.2007.084731.

14. Yu W, Guo X, Xu W. An improved score interval with a modified midpoint for a binomial proportion. J Stat Comput Simul. 2014;84:1022–1038. doi.org/10.1080/00949655.2012.738211

15. Wilson EB. Probable Inference, the Law of Succession, and Statistical Inference. Journal of the American Statistical Association. June 1, 1927;22(158):209-212. DOI: 10.2307/2276774

16. Roldán-Nofuentes JA. Simultaneous Comparison of Sensitivities and Specificities of Two Diagnostic Tests Adjusting for Discrete Covariates. Mathematics 2021;9:2029. doi.org/10.3390/math9172029

17. Godoy MCB, Odisio EGLC, Truong MT, de Groot PM, Shroff GS, Erasmus JJ. Pulmonary Nodule Management in Lung Cancer Screening: A Pictorial Review of Lung-RADS Version 1.0. Radiol Clin North Am. May 2018;56(3):353-363. doi: 10.1016/j.rcl.2018.01.003.

18. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395–409. doi: 10.1056/NEJMoa1911793.

19. Lee HY, Lee KS. Ground-glass opacity nodules: histopathology, imaging evaluation, and clinical implications. J Thorac Imaging 2011;26(2):106–118. doi: 10.1097/RTI.0b013e3181fbaa64.

20. Midthun DE, Swensen DJ, Jett JR. Approach to the solitary pulmonary nodule. Mayo Clin Proc 1993;68:378-385. doi: 10.1016/s0025-6196(12)60136-0.

21. Centers for Disease Control and Prevention. National Center for Health Statistics. CDC WONDER Online Database, Compiled from Compressed Mortality File 1999-2016 Series 20 No. 2V, 2017.

22. Revel MP, Mannes I, Benzakoun J, Guinet C, Léger T, Grenier P, et al. Subsolid lung nodule classification: A CT criterion for improving interobserver agreement. Radiology. 2018;286:316. doi: 10.1148/radiol.2017170044.

23. MacMahon H, Austin JH, Gamsu G, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. Radiology 2005;237(2):395–400. doi: 10.1148/radiol.2372041887.

24. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early lung cancer action project: a summary of the findings on baseline screening. Oncologist. 2001;6:147-152. doi: 10.1634/theoncologist.6-2-147.

25. Hollings N, Shaw P. Diagnostic imaging of lung cancer. Eur Respir J. 2002;19:722-742. doi: 10.1183/09031936.02.00280002.

26. Zerhouni EA, Stitik FP, Siegelman SS, et al. CT of the pulmonary nodule: a cooperative study. Radiology. 1986;160:319-327. doi: 10.1148/radiology.160.2.3726107.

27. Gurney JW, Lyddon DM, McKay JA. Determining

the likelihood of malignancy in solitary pulmonary nodules with Bayesian analysis. II. Application. Radiology 1993;186(2):415–422. doi: 10.1148/radiology.186.2.8421744.

28. Winer-Muram HT. The solitary pulmonary nodule. Radiology 2006;239(1):34–49. doi: 10.1148/radiol.2391050343.

29. Zhao YR, Xie X, de Koning HJ, Mali WP, Vliegenthart R, Oudkerk M. NELSON lung cancer screening study. Cancer Imaging. 2011;11:S79-S84. doi: 10.1102/1470-7330.2011.9020.

30. Ko JP, Bagga B, Gozansky E, Moore WH. Solitary Pulmonary Nodule Evaluation: Pearls and Pitfalls. Seminars in Ultrasound, CT and MRI. June 1, 2022;43(3):230-245. doi: 10.1053/j.sult.2022.01.006.

31. Roldán-Nofuentes JA. Compbdt: an R program to compare two binary diagnostic tests subject to a paired design. BMC Medical Research Methodology. June 5, 2020;20(1):143. doi: 10.1186/s12874-020-00988-y.

32. Li Y, Hu H, Wu Z, Yan G, Wu T, Liu S, et al. Evaluation of models for predicting the probability of malignancy in patients with pulmonary nodules. Biosci Rep. February 28, 2020;40(2). doi: 10.1042/BSR20193875.

33. Soardi GA, Perandini S, Motton M, Montemezzi S. Assessing probability of malignancy in solid solitary pulmonary nodules with a new Bayesian calculator: improving diagnostic accuracy by means of expanded and updated features. Eur Radiol. January 2015;25(1):155-162. doi: 10.1007/s00330-014-3396-2. Epub 2014 Sep 3

34. Fierro CAC, Naranjo M, Dueñas JAC, Trigos LAC, Sarzosa FA, Ramirez MRB, et al. Etiology of false positives of 18F-FDG PET-CT in mediastinal and hilar lymph nodes with surgical biopsy in oncology patients. Revista Colombiana de Cancerología. December 30, 2022;26(4):412-419. doi.org/10.35509/01239015.855

35. McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med. September 5, 2013;369(10):910-919. doi: 10.1056/NEJMoa1214726.

36. Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. Arch Intern Med. 1997;157(8):849-855. doi.org/10.1001/archinte.157.8.849

37. Herder GJ, van Tinteren H, Golding RP, Kostense PJ, Comans EF, Smit EF, et al. Clinical Prediction Model to Characterize Pulmonary Nodules: Validation and Added Value of 18F-Fluorodeoxyglucose Positron Emission Tomography. Chest. 2005;128(4):2490-2496. doi: 10.1378/chest.128.4.2490.

38. Gould MK, Ananth L, Barnett PG, Veterans Affairs SNAP Cooperative Study Group. A clinical model to estimate the pretest probability of lung cancer in patients with solitary pulmonary nodules. Chest. 2007;131(2):383-388. doi: 10.1378/chest.06-1261.

39. Zhang K, Wei Z, Nie Y, Shen H, Wang X, Wang J, et al. Comprehensive Analysis of Clinical Logistic and Machine Learning-Based Models for the Evaluation of Pulmonary Nodules. JTO Clin Res Rep. 2022;3(4):100299. doi: 10.1016/j.jtocrr.2022.100299.

40. Baldwin DR, Gustafson J, Pickup L, Arteta C, Novotny P, Declerck J, et al. External validation of a convolutional neural network artificial intelligence tool to predict malignancy in pulmonary nodules. Thorax. 2020;75(4):306-312. doi: 10.1136/thoraxjnl-2019-214104.

41. Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, Wiener RS. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. May 2013;143(5 Suppl). doi: 10.1378/chest.12-2351. PMID: 23649456; PMCID: PMC3749714. doi: 10.1378/chest.12-2351.

42. Erhunmwunsee L, Tong BC. Preoperative Evaluation and Indications for Pulmonary Metastasectomy. Thorac Surg Clin. February 2016;26(1):7-12. doi: 10.1016/j.thorsurg.2015.09.002. PMID: 26611505; PMCID: PMC5142629.

43. Petrella F, Diotti C, Rimessi A, Spaggiari L. Pulmonary metastasectomy: an overview. J Thorac Dis. October 2017;9(Suppl 12):S1291-S1298. Doi: 10.21037/jtd.2017.03.175. PMID: 29119017; PMCID: PMC5653506. doi: 10.21037/jtd.2017.03.175