Incidence of Incidental Lung Cancer Detected in Thoracic Computed Tomography During the COVID-19 Pandemic: A Perspective on Lung Cancer Screening in Turkiye

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ABSTRACT

There are risk-based screening programs for lung cancer screening in the world. There is no screening program for lung cancer in Turkiye. The aim of our study was to investigate the incidence of pulmonary nodules and lung cancer detected incidentally with computed tomography scans performed due to the COVID-19 pandemic. Thoracic Computed Tomography (CT) scans performed with suspicion of COVID-19 between 11.03.2020 and 31.03.2022 were analyzed as a single-center and retrospective cohort. Patients with a history of previously diagnosed malignancy or in the follow-up with solitary pulmonary nodules were excluded. A total of 2381 patients were examined, and the mean age was 50.42± 17.03 years. While 267 (11.2%) patients had solitary pulmonary nodules on CT scans, 66 (2.7%) patients were diagnosed with lung cancer. Patients were categorized according to age. The risk of pulmonary nodules increased 1.92-fold between the ages of 51-60, 2.26-fold between the ages of 61-70, and 2.05-fold above the age of 70 compared to age 50 ($p< 0.001$ for all). Compared to age 50, the risk of developing lung cancer increased 10.3-fold between the ages of 51-60, 33.5-fold between the ages of 61-70, and 34.5-fold above the age of 70 ($p< 0.001$ for all). In our study, we observed that the risk of incidental detection of pulmonary nodules and lung cancer increased with the age above 50. With this cohort study, we aimed to provide an overview of lung cancer risk prediction models and applications for lung cancer screening.

Keywords: Solitary Pulmonary Nodule, COVID-19, Lung Cancer, Screening

INTRODUCTION

Pulmonary nodules are common findings on Computed Tomography (CT) scans and the detection rate of incidental pulmonary nodules has increased with the widespread use of CT. Although most incidental pulmonary nodules (IPN) are benign, some are early-stage lung cancer.[1,2] Although early-stage cancer rates have been reported to range from 5.5-23% in studies[3,4], the incidence of lung cancer in a large screening cohort was reported to be 645 per 100,000 person-years.[5] Lung cancer is the leading cause of cancer-related death worldwide.[6,7] Considering that most of the cases are detected in advanced stages with poor prognosis[8], early detection is recognized as the most important factor in reducing mortality due to lung cancer.[9]. The implementation of lung cancer screening programs using low-dose CT (LDCT) in high-risk individuals aims to detect lung cancer as early as possible.

In 2021, the lung cancer screening program in the United States of America (USA) identified patients aged 55-80 years, who had smoked at least one pack of cigarettes a day for 20 years and were still smokers or had quit smoking within 15 years as a high-risk group and recommended annual lung cancer screening for these patients.[10] The National Lung Screening Trial (NLST) reported a relative risk reduction of 20% in lung cancer mortality with lung cancer screening.[5] In the Nelson study, lung cancer mortality in the high-risk group was found to be significantly lower in those who underwent CT screening compared to those who were not screened.[11] Risk-based lung cancer screening is an approach that defines screening eligibility based on individual risks. There is currently no screening program for lung cancer in Turkiye.

In the diagnostic approach recommended by the Ministry of Health in our country during the COVID-19 pandemic, it was stated that CT is a sensitive diagnostic approach in the early period in patients with negative polymerase chain reaction (PCR) tests and suspected COVID-19. It was also recommended in the guideline that thorax CT should be performed to support faster evaluation of these patients.[12] Therefore, during the COVID-19 pandemic in our country, CT scans were performed in a high population including COVID-19 suspected cases without any risk discrimination. The aim of our study was to investigate the frequency of incidental pulmonary nodules and lung cancer detected by CT scans due to COVID-19 during the COVID-19 pandemic. The study also aimed to investigate the frequency of incidentally detected nodules, determine the risk groups and pioneer screening programs for lung cancer in our country.

PATIENTS AND METHODS

Study Population

Thorax CT scans performed with suspicion of COVID-19 were analyzed as a single-center and retrospective cohort study, between 11.03.2020 and 31.03.2022. All patients who applied to the COVID-19 outpatient clinic and underwent thorax CT scan were included in the study. The COVID-19 outpatient clinic was a clinic in a large city, a reference hospital in the Aegean Region in terms of chest diseases, where all patients who came without referral were accepted and patients were aged 18 years and older. Patients who were diagnosed with lung cancer before admission, patients who were in a follow-up program for pulmonary nodules before admission, and patients for whom adequate medical clinical data could not be obtained through the hospital information system were excluded from the study (Figure 1).

Age, gender, smoking history, comorbid diseases, and pulmonary nodule detection status of 2381 patients were recorded. In 267 patients, who had pulmonary nodules, nodule characteristics and lymph node involvement were recorded. In 72 patients who underwent biopsy, a whole body scan (PET/CT + brain magnetic resonance imaging or brain + thorax + whole abdomen CT) was performed before the biopsy, and metastasis status was recorded. According to TNM 8th staging system of 66 patients with lung cancer[13] stage and histopathologic type were recorded.

All thorax CT scans were evaluated and reported by a radiologist. Solitary pulmonary nodules are defined as circumscribed, circular opacities ≤ 3 cm in diameter, surrounded by lung parenchyma.[14] Nodules may contain solid and ground-glass components. A solid component is the part of the nodule that covers the bronchovascular structures, whereas a ground-glass component is the part of the nodule that is denser than the ground but does not cover the underlying vascular structures. A solid nodule is defined as focal opacities consisting entirely of a solid component, while a subsolid nodule includes partial solid and pure ground-glass nodules.[14-16] The solid/subsolid component of the detected nodules was recorded.

Computed Tomography Technique

All CT scans were performed with a Hitachi Supria 64-slice multidetector CT (multislice CT). The acquisition parameters were 120 KV, 150-350 mA, slice thickness of 1.25 mm. The scans were performed without a contrast.

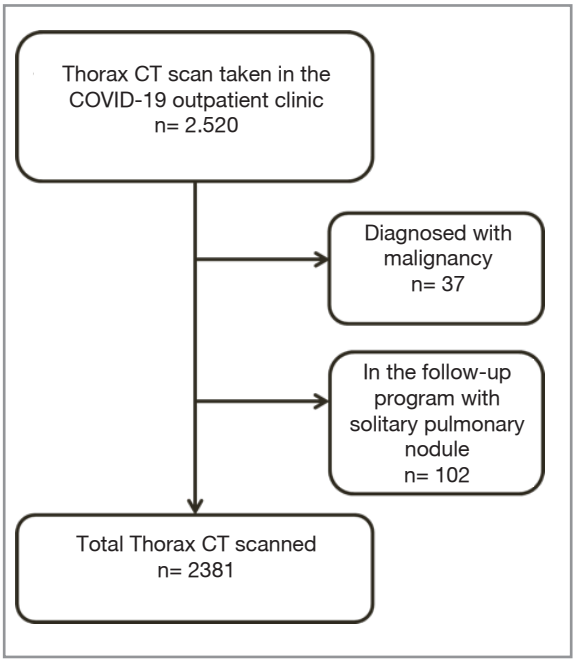


Figure1. Patient disposition chart

Ethical Approval: This study was approved by the Institutional Review Board of Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital (Approval number/date: 2021/8; September 22, 2021). All procedures performed in studies involving human participants were carried out following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL). The conformity of continuous variables to normal distribution was investigated by graphical exploration, normality tests, and sample size. Patient characteristics were presented by means (SD), median (IQR), or numbers and percentages of the total. Comparisons of independent groups; variables fitting the normal distribution were compared with the "student t" test and variables not fitting the normal distribution were compared with the nonparametric method "Mann-Whitney U" test. Variables associated with the frequency of pulmonary nodules and lung cancer were analyzed by univariate analysis. Receiver Operating Characteristic (ROC) analysis was used to determine the optimum cut-off for lesion size. Variables found to be statistically significant in univariate analysis were analyzed by multivariate analysis using a logistic regression test.

In all statistical comparison tests, the first-type margin of error was set as α: 0.05, and two-tail tested and the difference between the groups was considered statistically significant if the "p" value was less than 0.05.

RESULTS

A total of 2381 patients were examined, 1365 (57.3%) of the patients were male and the mean age was 50.42 ± 17.03 years. Solitary pulmonary nodules were found in 267 (11.2%) patients. A total of 72 (3%) patients underwent biopsy. No major complications were observed in any patient after biopsy. A histopathologic diagnosis of malignancy was made in 69 (2.9%) patients with solitary pulmonary nodules. Among the patients who underwent biopsy, benign causes were found in 3, lung cancer in 66, and extra thoracic organ malignancy in 3 patients (Table 1).

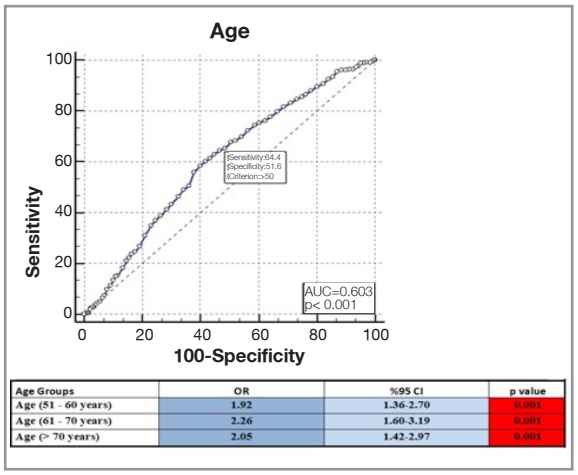
Patients were categorized according to age and the cut-off value was taken as 50. Starting from the age of 50 years, the incidence of pulmonary nodules increased with each 10-year increase in age. There was a 1.92-fold increase in the incidence of pulmonary nodules between the ages of 51-60, 2.26-fold between the ages of 61-70, and 2.05-fold above the age of 70 (for all, $p< 0.001$) (Figure 2). The incidence of lung cancer increased with each 10-year increase in age starting from the age of 50 years. There was a 10.3-fold increase between the ages of 51-60, 33.5-fold between the ages of 61-70, and 34.55-fold above the age of 70 (for all $p< 0.001$) (Figure 3).

In patients with pulmonary nodules (n= 267), risk factors for malignancy were analyzed. The optimum cut-off value for lesion size was determined as 2 cm (AUC: 0.950; 95% CI: 0.917- 0.973; $p< 0.001$). In univariate analysis, age older than 50 years, male gender, smoking or a history of smoking, presence of a history of chronic disease, nodule size above 2 cm, presence of a single nodule,

Table 1. Demographic characteristics of patients

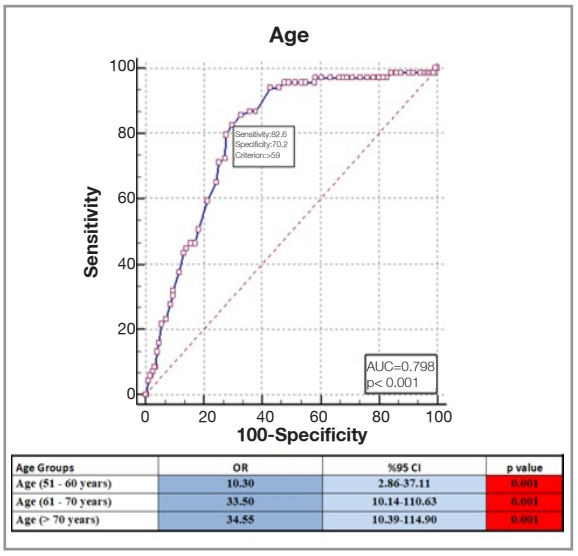
CHARACTERISTICS*		**n (%)**
Age (mean ± SD)		50.42± 17.03
Gender	Male	1365 (57.3)
Smoking History n (%)	Ex smoker	48 (2.01)
(n= 2381)	Never	30 (1.25)
	Current smoker	57 (2.39)
Comorbid Disease n (%)	COPD	61 (2.56)
(n= 2381)	Asthma	21 (0.88)
	Cardiac Disease	34 (1.42)
	Hypertension	6 (0.25)
	Diabetes Mellitus	3 (0.12)
	Others	5 (0.20)
Nodule	Yes	267 (11.2)
(n= 2381)	No	2114 (88.8)
Nodule	Single	133 (49.8)
(n= 267)	Multiple	134 (50.2)
Nodule	Solid	218 (81.6)
(n= 267)	Subsolid	49 (8.4)
T status -Tumor size	>7 cm	25 (9.4)
(n=267)	5-7 cm	16 (6)
	4-5 cm	7 (2.6)
	3-4 cm	11 (4,1)
	2-3 cm	28 (10.5)
	1-2 cm	47 (17.6)
	0.5-1 cm	133 (49.8)
N Status -Lymph node	N3	14 (5.24)
(n= 267)	N2	45 (16.8)
	N1	8 (2.99)
	N0	200 (74.97)
M status -Metastasis	M1a+b+c	40 (55.5)
(n= 72)	M0	32 (44.4)
Stage	Stage I	2 (3.03)
(n= 66)	Stage II	2 (3.03)
	Stage III	22 (33.3)
	Stage IV	40 (60.64)
Biopsy	Yes	72 (26.9)
(n= 267)	No	195 (73.1)
Histopathological Diagnosis n (%)	Adenocarcinoma	21 (29.2)
(n= 267)	Squamous Cell Cancer	20 (27.8)
	NSCLC	13 (18.1)
	SCLC	8 (11.1)
	Large-cell Lung Cancer	3 (4.2)
	Adenosquamous	1 (1.4)
	Testicular Tumor	1 (0.37)
	Lymphoma	2 (0.74)
	Benign	3 (4.16)

** Age, gender, smoking history, comorbid diseases and pulmonary nodule detection status of 2381 patients were recorded. In 267 patients diagnosed with pulmonary nodule, nodule characteristics and lymph node involvement were recorded. In 72 patients who underwent biopsy, metastas status was recorded. TNM staging was performed in 66 patients diagnosed with lung cancer.*
COPD= Chronic obstructive pulmonary disease, NSCLC= Non-small cell lung cancer, SCLC= Small cell lung cancer



Age Groups	OR	%95 CI	p value
Age (51 - 60 years)	1.92	1.36-2.70	0.001
Age (61 - 70 years)	2.26	1.60-3.19	0.001
Age (> 70 years)	2.05	1.42-2.97	0.001

Figure 2. Incidence of pulmonary nodules associated with increasing age



Age Groups	OR	%95 CI	p value
Age (51 - 60 years)	10.30	2.86-37.11	0.001
Age (61 - 70 years)	33.50	10.14-110.63	0.001
Age (> 70 years)	34.55	10.39-114.90	0.001

Figure 3: Incidence of lung cancer associated with increasing age

solid component of the nodule, and lymph node involvement were found to be statistically significant variables in the development of malignancy (for all, p= 0.001). Variables found to be statistically significant in univariate analysis were analyzed in multivariate analysis. Age, smoking history, tumor size, and lymph node involvement were statistically significant variables in multivariate analysis (p= 0.019; p= 0.006; p= 0.001; p= 0.001, respectively) (Table 2).

DISCUSSION

The aim of this cohort study was to provide an overview of lung cancer risk prediction models and applications for lung cancer screening. Lung cancer risk prediction models are based on the identification of high-risk groups for lung cancer screening. Some risk models have been developed to predict the malignancy probability of solitary pulmonary nodules to optimize the frequency of screening of eligible individuals. In our study, we observed that the risk of incidental detection of pulmonary nodules and lung cancer above the age of 50 years increased. In addition, age, smoking history, lesion size, and lymph node involvement were identified as risk factors for incidentally detected nodules, and their presence was associated with the development of malignancy.

Age is an important risk factor in the development of lung cancer.[17] Because of this, the age range included in screening studies is an important determinant of the outcome of screening. In Nelson[11], NLST[5], and in the French lung cancer screening study (Depiscan)[18], patients aged 50-75 years were identified as the target group, whereas in the German Lung Cancer Screening Intervention (LUSI)[19], 50-69 years, and in the Danish Lung Cancer Screening Study (DLCST)[20], the population between 50-70 years of age was determined as the target group. In three different screening studies conducted in Italy (ITALUNG[21]), the age range was narrowed compared to other studies and the age range was 55-69 years, in MILD[22], the age range was wider and included cases under the age of 55 and over the age of 70. In the DANTE study[23], on the other hand, cases between 60-74 years of age were identified as the target group, and an older population was examined than in other screening studies. Our study is not a lung cancer screening study. Therefore, a target group was not selected. However, in our study, an increase in the detection rate of lung cancer was observed with each 10-year increase in age starting from the age of 50. Similar to lung cancer screening studies, our study showed that age is an important risk factor in the development of lung cancer. Our study has shown that 50 years of age is an important cut-off in the selection

Table 2. Univariate and multivariate analysis of factors affecting the development of lung cancer

	Univariate		Multivariate	
	HR (%95 CI)	p value	HR (%95 CI)	p value
Age (> 50 / ≤ 50 years)	19.09 (5.80-62.78)	0.001	7.07 (1.37-36.27)	0.019
Gender (Male / Famale)	5.63 (2.45-12.95)	0.001		
Smoking History (Yes / No)	7.55 (4.05-14.07)	0.001	4.50 (1.55-13.07)	0.006
Comorbid Disease (Yes / No)	7.20 (3.85-13.48)	0.001		
COPD (Yes / No)	6.81 (3.63-12.74)	0.001		
Cardiac Disease (Yes / No)	4.63 (2.19-9.77)	0.001		
Tumor size (> 2 cm / ≤ 2 cm)	61.29 (25.24-148.79)	0.001	18.50 (5.18-55.37)	0.001
Lymph node involvement (N1-N2-N3/N0)	66.78 (28.68-155.47)	0.001	16,89 (5.75-49.60)	0.001
Nodule (Single / Multiple)	2.55 (1.43-4.52)	0.001		
Nodule (Solid / Subsolid)	21.76 (2.94-160.93)	0.001		

COPD= Chronic obstructive pulmonary disease, CI= Confidence Interval

of the target group and it is thought that this cut-off may be important in screening studies.

When the incidence analyses in lung cancer screening studies were analyzed, the incidence of lung cancer in the NLSTT at 10-year follow-up was 5.58 cases per 1000 person-years in the screening group and 4.91 cases per 1000 person-years in the control group.[5] In a study conducted in Denmark (DLCST), 5.1 cases were reported per 1.000 people/year and 2.7 cases per 1.000 people/year in the control group[20] and in ITALUNG study, 49.9 cases were reported per 10.000 people-year in the screening group and 53.7 cases per 10.000 in the control group (21). A total of 1994 participants underwent CT scanning for lung cancer screening in the United Kingdom and 42 participants (2.1%) were diagnosed with lung cancer.[24] In our study, 2381 CT scans were performed and 66 people (2.7%) were diagnosed with lung cancer. The differences in the target populations determined in the studies and the different numbers of screened populations are thought to be the reason for the difference in the number of lung cancers detected.

The success of screening studies is associated with the early detection of lung cancer in screening groups. Curative treatment options in early-stage lung cancer can provide a significant difference in 5-year mortality compared to advanced lung cancer.[9] In NLST and Nelson, the percentage of stage IA and stage IB lung cancers in the screening group was the highest among cancers diagnosed.[5,11] In Nelson, almost half of the lung cancers detected in the control group were stage IV.[11] In DLST[20] and ITALUNG[21], early-stage disease was more likely to be detected in the screening groups. However, unlike in Depiscan, stage IIIB and IV patients were predominant in the screening group.[18] The authors reported that selection bias may have contributed to these results, although the reason for this was not clear. In our study, the majority of patients diagnosed with lung cancer were stage III and IV patients. In addition, similar to our study, the most common histopathologic type was adenocarcinoma.[11,18-21]

There are some question marks in the implementation of screening programs in large groups. One of these is false positive rates. In our study, the false positive rate was 0.12% in the whole population (3/2381). In NLST[5], the false positive rate was 1.7%, 1.2% in Nelson[11], 7.9% at baseline in the DLCST, and 1.7%, 2.0%, 1.6%, and 1.9% in the next four screening rounds, respectively.[20] In the CISNET modeling study, when the 2021 US Preventive Services Task Force (USPSTF) criteria and the 2013 USPSTF criteria are updated, a decrease in the per capita false positive rate during lifetime screening is expected (1.9; 2.2, respectively).[25] Considering that the aim of our study was not lung

cancer screening and that CT scanning was performed in a smaller group compared to screening studies, the false positive rates are considered to be at an acceptable level. It is thought that false positives can be prevented by clearly identifying the target population and determining the malignancy criteria in IPNs.

There is also an increase in incidental findings in screening at older age. Extrapulmonary findings commonly detected in NLST included coronary artery calcification, aortic aneurysms, emphysema, and infectious and inflammatory processes. In addition, cancers involving the kidney, thyroid, or liver were diagnosed in 0.39% of NLST participants during screening.[26] In our study, extrapulmonary malignancy (testicular tumor in 1 patient and lymphoma in 2 patients) was diagnosed in 3/2381 patients. Additional incidental findings other than lung cancer lead to many additional evaluations, including additional imaging, consultation, and invasive procedures.[27] The benefit/harm balance of additional incidental findings other than lung cancer remains unclear.

The risks of overdiagnosis and radiation exposure in lung cancer screening are harmful, although the exact magnitude of the radiation is uncertain. The decision to perform screening should include a thorough discussion of the potential benefits, limitations, and harms of screening. A major source of controversy surrounding lung cancer screening with LDBT is overdiagnosis, i.e. the detection of cancers that would never have become symptomatic if they had not been detected because they never grew, or grew slowly, or because death from another cause intervened.[28,29] The other harmful effect is radiation exposure. One study indicated that the association between LDBT and radiation-induced cancer development is not directly measurable and is a long-term entity and should be evaluated in future analyses.[30] In another study, the lifetime cancer risk from radiation with 10 LDBTs per year was estimated to be 0.26 to 0.81 major cancers for every 1000 people screened.[31] The reduction in lung cancer mortality requires a long-term evaluation, comparing the harms from positive screening results and overdiagnosis, as well as the costs.

Our study has limitations. First, due to the retrospective design of our study, the cumulative amount and duration of smoking, which is one of the most important risk factors for lung cancer, could not be reached in every patient. In addition, family history of malignancy and environmental exposure, which are other risk factors for malignancy, could not be questioned, which was another limitation of our study. In our study, histopathologic results were obtained in (72/267) of the patients with pulmonary nodules who underwent biopsy. The other nodules (195/267) were included in the pulmonary nodule follow-up program. Due to the retrospective nature of the study, there is a possibility that patients with pulmonary nodules who were included in the follow-up program may have lung malignancy during the follow-up process, which may change the incidence rates of lung cancer. Lung cancer screening studies worldwide are performed with LDBT, but since our study was not performed for lung cancer screening, all CT scans were performed with standard-dose CT. Although there are screening programs for malignancies such as breast, prostate, and colon cancer in our country, there is no screening program for lung cancer. In the future, a screening study can be planned in a pilot region based on the identified risk groups. Although it is difficult to generalize the results of our study to the whole population, risk factors for lung cancer have been demonstrated and risk-based screening programs can be implemented in our country in the future.

In Conclusion, in our study, we observed that the risk of incidental detection of pulmonary nodules and lung cancer increased with the age above 50. In addition, age, smoking history, lesion size, and lymph node involvement were found to be associated with the development of malignancy. Our findings are consistent with the risk factors of international lung cancer screening studies. The similarity of risk factors with international screening studies suggests that these criteria can also be used in our country. With this cohort study, we aimed to provide an overview of lung cancer risk prediction models and practices for lung cancer screening. We demonstrated the effect of age on the development of lung cancer in the selection of risk groups for lung cancer pilot studies to be conducted in our country.

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Seher Susam	0000-0003-2021-4594
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