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ORIGINAL ARTICLE

The Cost-effectiveness of National Lung Cancer Screening in Türkiye

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OBJECTIVE

The aim of this study is to analyze the cost-effectiveness of the national lung cancer screening program in Türkiye.

METHODS

In this cost-effectiveness model, the most likely protocol to be used after implementing a lung cancer survey for Türkiye, the NELSON protocol, was used to make a comparison with the "no screening" case. This protocol involves individuals screened using low-dose computed tomography (LDCT). The model is anticipated to simulate 14 screening rounds, assuming an age range of 50–74 for lung cancer and 58 years for the screening program participants. The main outputs of the model were total life years gained (LYG), quality-adjusted life years (QALYs) gained in the screening arm, and the incremental cost-effectiveness ratio (ICER).

RESULTS

The analyses revealed a total QALY gained in the screening arm of 12,465,801 vs. a QALY gained of 12,149,148 in the comparator no screening arm. The incremental QALY value was estimated to be 316,654. The total LYG were 15,954,511 and 15,370,671 in the screening and no screening arms, respectively, resulting in an incremental LYG of 583,840. With lung cancer screening, stage III and IV cancer were identified in earlier phases in 13,636 cases. Prevented early deaths were 7,576. For the lung cancer screening program, the cost per QALY is $571, and the cost per LYG is $310.

CONCLUSION

Based on the results, implementation of the national lung cancer screening program was found to be very cost-effective for Türkiye.

Keywords: Life year gains; lung cancer; lung cancer screening; NELSON; QALYs.

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INTRODUCTION

Cancers are among the leading causes of death and one of the most important community health problems worldwide, responsible for approximately 10 million deaths, or one in every six deaths, in 2020.[1] According to the data from the World Cancer Research Fund (WCRF), 18.1 million new cases of cancer were identified worldwide in 2020, 9.3 million of which were found in men and 8.8 million in women. Lung cancer constitutes 15.4% of cancers seen in men and 8.8% in women, accounting for 12.2% of all cancers (2.2 million cases).[2] Lung cancer is responsible for approximately 25% of all cancer deaths.[3] Leading to 1.8 million deaths, lung cancer was the leading cause of cancer-related death in 2020.[1]

Around 30,000 new cases of cancer are diagnosed annually in Türkiye. The most frequent cancer type in men is lung cancer, while in women it ranks fifth. In 2017, the age-standardized rate of lung cancer in men was 56.7 per 100,000 versus 11.1 per 100,000 in women.[4] The lung cancer burden is high in Türkiye. According to Cicin et al.,[5] the total per-patient annual direct medical cost for small cell lung cancer was €8,772, and for non-small cell lung cancer, it was €10,167. The total annual direct medical cost was €497.9 million, the total annual indirect medical cost was €1.1 billion, and the total economic burden of lung cancer was €1.6 billion. Hospitalization/interventions (41%) and indirect costs (68.6%) were the major cost drivers for total direct costs and the overall economic burden of lung cancer, respectively.

The high mortality rate in lung cancer results from detecting the cancer in advanced stages, where treatment is more difficult and symptoms appear later.[3] The National Lung Screening Trial (NLST) based in the United States of America (USA) and the Netherlands-Belgium Randomized Lung Cancer Screening Trial (Nederlands-Leuvens Longkanker Screenings Onderzoek, NELSON) demonstrated that lung cancer screening (LCS) benefits lung cancer patients through mortality reduction attributed to early detection.[6–10] In addition, various cost-effectiveness studies estimated the incremental costs and benefits of implementing a national LCS program, finding that LCS was frequently assessed as cost-effective.

In this study, we aimed to analyze the anticipated clinical benefits and economic costs associated with implementing the national lung cancer screening program in Türkiye. The model estimates whether lung cancer screening using low-dose computed tomography (LDCT) can ensure favorable utilization of national resources based on the assumed willingness-to-pay (WTP) threshold for reimbursement in Türkiye.

MATERIALS AND METHODS

Model Overview

The structure of the model is a decision tree with an integrated Markov model (Appendix 1). The decision tree provides the model with estimates of the number of positive and negative scans and the distribution of lung cancer stages among patients. It presents two strategies: screening and no screening. In the screening strategy, the high-risk population will undergo LDCT scans, where lung cancers in various stages can be detected. How the screening participants transfer within the decision tree is determined by detectability and stage distribution based on the NELSON screening trials.

In the no screening arm, symptomatic patients with a clinical presentation are identified over time. How the no screening population transfers within the decision tree is informed by Türkiye-specific epidemiological data, such as lung cancer incidence and stage distribution. Screening participants without detected lung cancer will annually re-enter the screening arm in the decision tree until lung cancer detection. Individuals in the no screening arm without symptomatic lung cancer are diagnosed through clinical presentation and will annually re-enter the no screening arm in the decision tree until a lung cancer diagnosis (Appendix 1).

The natural endpoints of true positive lung cancer cases identified in each screening were evaluated by forming an analytic decision model with a Markov model integrated into the decision tree. The Markov model is structured as a multiple health condition model comprising pre-progression, post-progression, and death states to reflect actual clinical practice (Appendix 2).

The base case was adjusted to reflect a time horizon of the lifespan, allowing the model to investigate the effects of lung cancer screening for life-long high-risk individuals on both health benefits and costs. The primary health outcomes of this cost-effectiveness analysis (CEA) model are life years gained (LYG) and quality-adjusted life years (QALYs). Stage III and IV lung cancer cases prevented by lung cancer screening and mortality prevented by screening were assessed as the primary clinical outcomes.

Model Inputs

Model parameters are presented in Table 1. The parameters used included costs, benefit values, survival rates, mortality due to all available causes, distribution

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Table 1 Model parameters

National data	**PSA distribution**	**NELSON data**
Lung cancer stage distribution (without screening)	Dirichlet	Diagnostic strength of screening Distribution of lung cancer stages at screening Diagnostic study practices
Costs to gather participants	Gamma	
Screening costs		
Diagnosis costs		
Bronchoscopy		
Biopsy or cytologic analysis		
Chest radiography		
Chest Ct		
FDG-PET and CT		
Mediastinoscopy or mediastinotomy		
Thoracoscopy		
Thoracotomy		
Treatment costs by stages		
Drugs		
Indirect costs		
Productivity cost (absenteeism cost)		
Transportation cost		
Utility values	N/A	
Survival data by the stages		
Stage I		
Stage II		
Stage III		
Stage IV		
Progression data by the stages		
Stage I		
Stage II		
Stage III		
Stage IV		

	Base case values	
Variable	**PSA distrubition**	**Input value**
Target population	Gamma	85,279,553
Age between 50–74	Gamma	22.17%
Smoking rate male	Beta	44.07%
Smoking rate female	Beta	19.35%
Smoking rate	Beta	31.73%
Gender distrubition in total male	Gamma	50.08%
Gender distrubition in total female	Gamma	49.92%
Gender distrubition amond LC-patients -male	Gamma	69.56%
Gender distrubition amond LC-patients -female	Gamma	30.44%
Number of screening participants	Gamma	1,019,827
Time horizon		32
Threshold value		$28,587.76
Establishment cost of the screening center		External
Discount rate		
Costs		3.5%
Health outcomes		3.5%
Screening protocol modeled		NELSON
Age group		50–74
Total screening visits (rounds)		14
Lung cancer stage distribution	Drichlet	Expert opinion based on unpublished data
Utility values		Tramontano et al.[16]
UK tariffs		
Disease/progression-free survival		Clinical trials
Mortality rate		Including 2019 Türkiye life table

FDG-PET: Fluorodeoxyglucose pet scan; CT: Computed tomography; PSA: Probabilistic sensitivity analysis; LC: Lung cancer; UK: United Kingdom

Table 2 Utility values of lung cancer by stage

Trial	Country and method	Utility values			
		Stages			
		I	II	III	IV
Tramontano 2015[16]	2344 UK NSCLC+SCLC SF-6D*	0.71	0.68	0.67	0.66

*: UK tariff used in the study. UK: United Kingdom; NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer; SF-6D: Short Form 6 Dimensions

of lung cancer stages, mortality rates due to lung cancer, and the distribution of screening stages. All-cause mortality was derived from Türkiye life tables.

The NELSON screening protocol was used for comparison with the "no screening" case since it is the most likely protocol to be adopted when LCS is implemented in Türkiye. The data on the distribution of lung cancer stages in the no screening group, which serves as the comparator arm, came from a multicenter dataset in Türkiye that has not yet been published. These data were validated by their proximity to clinical data reviewed by an expert panel. Validation was conducted by comparing the averages of other country data and unpublished data from Türkiye.

All indirect cost data were generated to reflect needs based on a societal perspective for Türkiye, while medical direct costs are aligned with a collectively funded national payer. Costs and effectiveness were subject to a 3.5% annual discount based on the base case analysis. The WTP threshold is taken as $28,587.76 based on the World Health Organization (WHO) recommendation of up to three times the Gross Domestic Product (GDP) per capita of the relevant country.

Patient Population & Inclusion Criteria

The target population in the model's base case analysis was defined as smokers aged 50–74 or those who quit smoking within the past 20 years.[11] Turkish population size is 85,279,553, and the eligible population is 18,906,477 who are 50–74 years old. The smoking rate is calculated as 31.7% based on the smoking rate of females (19.35%) and males (44.07%) in Türkiye.[12,13] Therefore, the population in the study was realized to be 1,019,827. The rate of compliance for screening participation was established as 17%. This rate of compliance was estimated using colorectal cancer participation rates (occult blood in the stool) in Türkiye.[12,13] The time horizon for analysis was set to 32 years to capture 81.3 years, the predicted lifetime in Türkiye.[14] (Table 1).

A panel of experts was formed for the validation of base case data for Türkiye, and the clinical inputs reflected the opinions of oncology, radiology, and chest disease specialists from six different tertiary healthcare centers and their clinical experiences for data utilization. Fourteen screening rounds were anticipated in the model by the experts, assuming a median age of 60 for lung cancer and 58 for the participants. Average age data from experts' clinical experience fits within the range of the NELSON protocol. In the current model, modeling was performed based on the NELSON protocol for the base case. All data on lung cancer were obtained from the expert panel as representative data for Türkiye. Utility values were taken from the UK model. This was considered a limitation of the study. Up to 14 annual screens were modeled, which reflected the mean age of participants in the NELSON study, while the maximum inclusion age for a scan was 74 years.[15]

Utility Values

The benefit values, as measured by Tramontano et al.,[16] were used among patients in the United Kingdom (Table 2).

Costs

The cost data were calculated in line with the Social Security Institution (SSI) perspective, as it is a national reimbursement institution.[17] Cost data comprise LDCT setup costs, screening costs, and treatment costs. There are no building costs, as existing cancer screening centers in Türkiye were considered. As of 2020, there were 175 KETEMs (Cancer Early Diagnosis, Screening and Education Centers) and 173 Tuberculosis Fighting Associations in various regions of Türkiye. The cost of a computed tomography (CT) device is approximately $410,000–$510,000, and annual service costs are $99,393.[18] The average time required to use a device is around 10 minutes per patient.

For cost estimation, the cost of 11 additional devices in the seven regions of Türkiye or the average CT unit cost was considered to be $5.09, as specified by the re-

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imbursement institution.[15,17] ($1 = TRY 17.49) Procedures for diagnostic studies and corresponding frequencies were drawn from both NELSON and included according to the costs in Türkiye.[15,19,20] Unit costs for each procedure, such as advanced imaging, bronchoscopy, percutaneous cytological analysis, or biopsy, were calculated in line with the Health Implementation Notification (HIN) issued by the reimbursement institution (SSI).[17] In conclusion, diagnostic costs per person were estimated by weighted frequencies per diagnostic procedure and used in the model.

Treatment costs were obtained from the study by Cicin et al.,[5] with validation of these data conducted through expert opinions.[11] These costs were reported in detail according to stages, including diagnosis and treatment costs, hospitalization costs, drug costs, side effect costs, and metastatic patient costs.

Survival

Five-year survival rates based on the stage were estimated to be 78.6% for Stage I, 54.9% for Stage II, 29.2% for Stage III, and 5.7% for Stage IV. For 10-year survival, the rates were 36.2%, 38.2%, 14.6%, and 0.7%, respectively, according to unpublished data validated by experts. Turkish single-age life tables of 2019[14] were included in the analysis to reflect the general population during survival estimations. The Stage III lung cancer progression-free survival curve was derived from a meta-analysis.[21]

Survival for Stage IV lung cancer was estimated from various studies, such as LUX-Lung 3, KEYNOTE-189, and Impower 133, which captured diverse treatments and lung cancer subtypes.[22–24] To ascertain the duration until disease progression exclusive of mortality, the lung cancer stage-specific overall survival (OS) rates were deducted from the respective disease and progression-free survival rates. These deduction rates were then employed to guide the transition from the pre-progression state to the post-progression state in the model. Overall survival rates for lung cancer at different stages upon diagnosis were informed by the Kaplan-Meier (KM) survival curves released by the International Association for the Study of Lung Cancer (IASLC).[25] In order to extend the analysis to a lifetime horizon, survival extrapolation was essential, employing the statistical methodology advocated by Guyot et al.[26]

Sensitivity Analysis

OWSA allows identifying the key model drivers, which are the parameters most influencing the ICER, by conducting deterministic changes of ±20% to parameter values. Results of the OWSA are presented in a table and a tornado diagram.

Using 1,000 simulations, parameters were sampled via Monte Carlo Simulation for probabilistic sensitivity analysis. Results are shown on the ICER plane. The number of times the results of an alternative are lower than a certain WTP threshold indicates the probability that lung cancer screening is cost-effective.

Scenario Analyses

Multiple scenarios were investigated. Initially, the cost-effectiveness of LCS was assessed from a societal viewpoint, encompassing indirect expenses like productivity loss and transportation costs, alongside the direct healthcare expenses from a healthcare system perspective. Productivity loss was computed using the human capital approach, comprising two components: premature patient deaths before retirement age and absence from the workforce due to illness.

Secondly, over the past decade, the adoption of novel medications, particularly in advanced-stage lung cancer, has risen in clinical practice, leading to enhanced patient outcomes but possibly at higher treatment expenses for this advanced stage. The impact of this trend on the cost-effectiveness of LCS was examined through scenario analysis.

Moreover, additional scenario analyses were carried out to explore the cost-effectiveness of LCS under diverse conditions, varying time horizons, and discounting rates. All scenarios resulted in an ICER below the WTP threshold.

RESULTS

Base-case Results

Clinical & Health Outcomes

With LCS, stage III and IV cancer were identified in earlier phases in 13,636 cases. 7,576 mortality events were prevented in the screened arm compared to the no screening arm (Table 3).

The analyses revealed a total QALY gained in the screening arm of 12,465,801 vs. a QALY gained of 12,149,148 in the comparator no screening arm. The QALY value was estimated to be 316,654. The total LYG in the screening arm was 15,954,511, while 15,370,671 life years were gained in the comparator no screening arm. The LYG value was estimated to be 583,840 (Table 4).

Cost Outcomes

The cost of screening was estimated from the payer perspective with a discount of 3.5%, and the total costs for the screening arm were identified to be $389,631,991. The screening cost was found to be

Table 3 Lung cancer stage & lung cancer deaths distributions by comparison arms

	Lung cancer stage distributions				Lung cancer deaths		
	Screening arm	Non- screening arm	Differences (additional lung cancer cases)	Stage III-IV cases averted	Screening arm	Non-screening Arm	Prevented early deaths
Total	132,764 (100%)	48,521 (100%)	84,244	13,636	26,917	34,493	7,576
Stage I	99,502 (75%)	3,348 (7%)	96,155		6,090	205	
Stage II	9,439 (7%)	7,715 (16%)	1,725		1,148	937	
Stage III	18,879 (14%)	13,343 (28%)	5,536		14,992	10,554	
Stage IV	4,944 (4%)	24,115 (50%)	-19,171		4,686	22,797	

Table 4 Results from the base case analysis

Costs ($)	Screening arm	No screening arm	Incremental/differences
Total Costs	389,631,991	208,778,554	180,853,437
Total QALYs	12,465,801	12,149,148	316,654
Total LYs	15,954,511	15,370,671	583,840
ICER	Costs per QALYs ($)	571	
	Costs per LYs ($)	310	
Costs ($)	**Screening arm**	**No screening arm**	**Incremental/differences**
Screening set-up	6,540,881	-	6,540,881
Screening	55,536,076	-	55,536,076
Diagnosis	5,012,740	1,279,109	3,733,631
Treatment	292,214,648	199,970,160	92,244,488
Stage I	172,153,685	5,781,954	166,371,731
Stage II	21,894,584	17,645,082	4,249,502
Stage III	71,700,018	50,100,107	21,599,911
Stage IV	26,466,361	126,443,018	- 99,976,657
Indirect	30,327,646	7,529,284	22,798,362
Health outputs	**Screening arm**	**No screening arm**	**Health gains**
QALYs	12,465,801	12,149,148	316,654
Stage I	1,045,449	35,096	1,010,353
Stage II	93,376	75,050	18,326
Stage III	57,523	40,060	17,463
Stage IV	7,498	35,758	-28,260
Non-diagnosed	11,261,955	11,963,183	-701,228
LYs	15,954,511	15,370,671	583,840
Stage I	1,529,109	51,332	1,477,777
Stage II	138,620	111,412	27,209
Stage III	86,735	60,404	26,331
Stage IV	11,360	54,179	-42,818
Non-diagnosed	14,188,686	15,093,345	-904,659

ICER: Incremental cost-effectiveness ratio

$55,536,076 for patients in the screening arm. The cost of diagnosis was $5,012,740, the cost of screening set-up was $6,540,881, treatment cost $292,214,648, cost of Stage I $172,153,685, cost of Stage II $21,894,584, cost of Stage III $71,700,018, cost of Stage IV $26,466,361, and indirect cost $30,327,646.

In the arm that is not screened, the total costs were identified to be $208,778,554. The cost of diagnosis was

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Table 5 Results of The One Way Sensitivity Analyses (OWSA)

	Results (ICER-$)		
Parameters	**Lower value**	**Upper value**	**Difference**
Utilities - LC stage III	947.23	386.96	560.26
Utilities - LC stage I	680.62	460.66	219.95
Treatment costs - stage I - first 90 days	503.72	595.20	91.54
Treatment costs - stage I - second year (per cycle)	510.41	588.56	78.16
Unit costs - CT scan	514.41	584.56	70.15
Treatment costs - stage IV - first 90 days	577.36	521.56	55.80
Treatment costs - stage IV - first year (per cycle)	577.24	521.67	55.57
Treatment costs - stage I - first year (per cycle)	531.22	567.70	36.42
Average distance to a hospital (mile)	534.31	564.61	30.30

ICER: Incremental cost-effectiveness ratio; LC: Lung cancer; CT: Computed tomography

$1,279,109, treatment cost was $199,970,160, treatment cost of Stage I $5,781,954, treatment cost of Stage II $17,645,082, treatment cost of Stage III $50,100,107, treatment cost of Stage IV $126,443,018, and indirect costs were $7,529,284.

The incremental costs were found to be $6,540,881 for screening setup, $55,536,076 for screening, $3,733,631 for diagnosis, $92,244,488 for treatment, $166,371,731 for Stage I, $4,249,502 for Stage II, $21,599,911 for Stage III, $-99,976,657 for Stage IV, and $22,798,362 for indirect costs (Table 4).

Cost-effectiveness Results

QALY and LYG were used as effectiveness values in the screened and non-screened arms to assess the cost-effectiveness of lung cancer screening in Türkiye. In the model, there were 316,654 QALYs and 583,840 life years gained in the screened arm compared to the no screening arm. The cost per QALY was $571, cost per life year gained was $310, and the incremental cost was $180,853,437 throughout the time horizon (32 years) of the analysis.

The willingness-to-pay (WTP) threshold value for Türkiye is $28,587.76, so the national lung cancer screening program is very cost-effective.

Sensitivity Analyses

In OWSA, the nine most effective model variables in the calculation were determined. Table 5 shows the lower and upper bound results and differences (Table 5). A graphical overview of these results is presented using a tornado diagram (Fig. 1). The parameters that had the greatest impact on ICER were lung cancer utility values, treatment costs, and tomography unit costs. All parameters are within the WTP threshold, showing the robustness of the study.

After 1,000 iterations, probabilistic sensitivity analysis resulted in an average ICER of $608 per QALY, which is below the WTP threshold (Fig. 2).

DISCUSSION

This modelling study investigated the cost-effectiveness of a nationwide LCS program with LDCT for high-risk populations in Türkiye.

To our knowledge, there are no studies in Türkiye regarding the cost-effectiveness of lung cancer screening programs. Compared to no screening in the target population at high risk for developing lung cancer, epidemiological data from Türkiye and the individuals to include in the cancer screening program were validated in the experts panel in this first study demonstrating predicted clinical benefits and economic costs regarding the implementation of the national lung cancer screening program based on the NELSON protocol. NELSON screening protocol was used for comparison with "no screening" case since this is the most likely protocol to be used as soon as a lung cancer screening is implemented. Fourteen screening rounds were anticipated in the model by the experts assuming an age between 50–74 for lung cancer and 58 for the participants. In the findings of the study, we see more cases of lung cancer cases in the screening arm. Also we found that the incremental cost-effectiveness of a LCS compared to no screening was $571 per QALY, with the total incremental costs of $180,853,437 for the life-long period (32 years) and QALYs of 316,654. Additionally, LCS detected 97,879 additional lung cancer patients in earlier stages (stage I and II) and 7,576 premature lung cancer deaths averted with LCS. The cost per LY is $310. Indirect costs were higher in the arm with screening than in

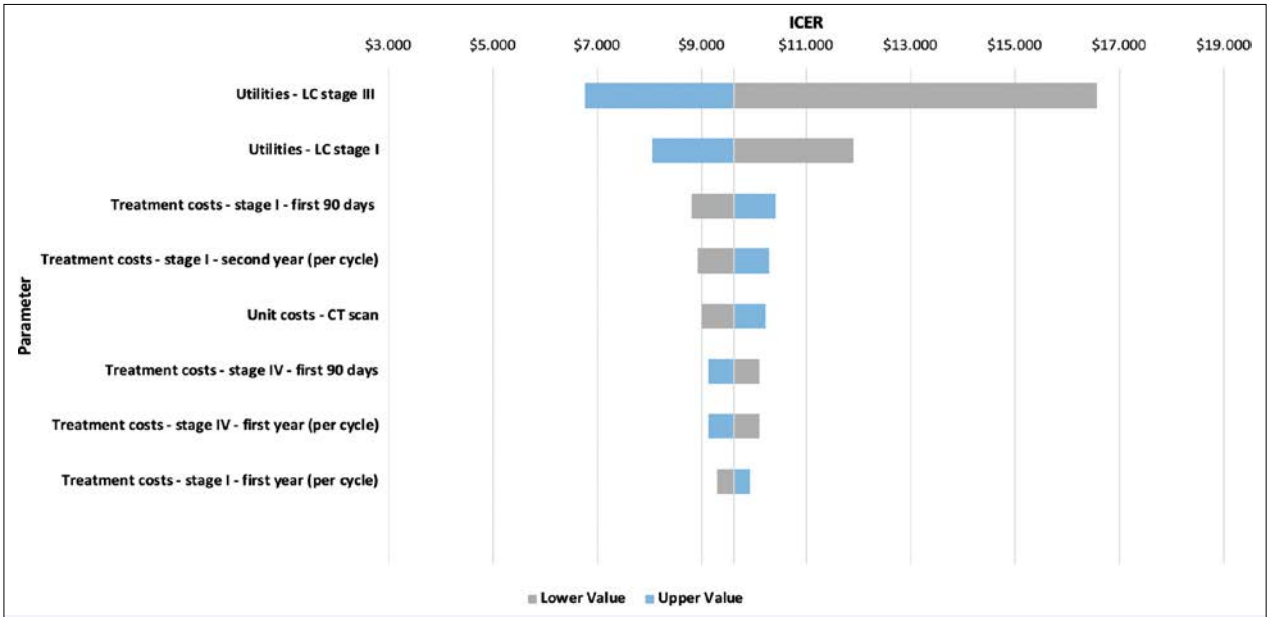

Fig. 1. Tornado diagram.
ICER: Incremental cost-effectiveness ratio; LC: Lung cancer; CT: Computed tomography.

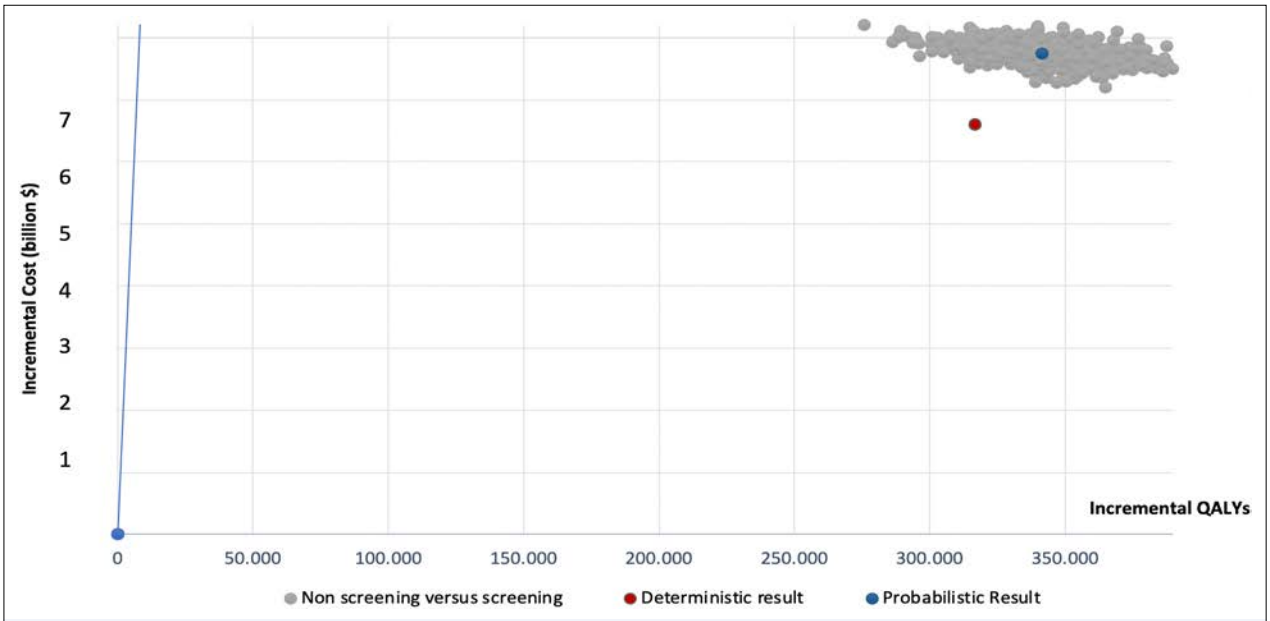

Fig. 2. ICER plane.
ICER: Incremental cost-effectiveness ratio; QALYs: Quality-adjusted life years.

the arm without screening. The most important reason for this is the size of the population to be screened, especially transportation costs. However, the values gained are significantly high considering the prevented cancer cases, early diagnosis and a longer and better quality of life for patients. It may be possible to reduce the screening population and costs with additional criteria to be determined by the authorities. The results were robust as indicated by sensitivity analyses. All analyses remained within the WTP threshold of $28,587.76 per QALY, a commonly used WTP in the Türkiye, providing further confidence in the results and the underlying model. The NELSON study demonstrated a 24–33% reduction in lung cancer mortality over a 10-year fol-

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low-up period, in our model shows very similar results. the lung cancer mortality reduction was estimated to be around 18% over a lifetime horizon, a figure notably consistent with outcomes observed in extensive clinical trials utilising low-dose CT for LCS. When we compare the ICER with the other countries' results, we can see big gaps based on $. The most important reason for this is Turkish health system. There is a general health insurance which covers all citizens in one umbrella and one authority, Social Security Institution, reimbursed all health expenditure in Türkiye instead of member of Social Security Insurance. Considering Turkish population is so high, it is not difficult to understand that the reimbursement for each person is at very low prices. Therefore, the resulting cost per QALY and cost per life years appear to be small. This suggests that low-dose CT is very cost-effective and should be considered by policy makers. The benefits of low-dose CT are also supported by many studies.

The target of screening for lung cancer is to detect the disease at the earliest stage possible while the tumor is small and limited to the thoracic cage, before it invades neighboring tissues, goes beyond the lung and/or causes symptoms in which treatment chances dramatically rise and the treatments are substantially successful. Early detection of lung cancer while it is small and localized is very important in reducing mortality.

The initial studies to reduce the mortality by early treatment and screening with lung X-ray for thorax tumors took place in 1950s.[27–30] A collaborative pilot study by the American Cancer Society (ACS) and Veterans Affairs (VA) identified 73 lung cancers in the screening of males older than 45 years of age (median age 62.8) using a questionnaire on smoking habits, occupational features and respiratory symptoms in addition to lung X-rays every 6 months for 3 years (1958–1961), and only 35% of these were resected. The 32-month survival in the ACS&VA study was a very low rate of 17%.[28] The Southern London Lung Cancer Study was conducted on 67,400 males over 45 years of age between 1959–1963. The rate of resections was reported to be 56% in 147 patients diagnosed, and the 4-year survival was 18% compared to the survival rate of 9% in that region.[29] The Northern London Lung Cancer Study carried out between 1960–1964 included 55,034 males over the age of 40. In this study, lung X-rays were performed for the control group in the beginning and end of the study, and the study group was screened every 6 months Annual mortality rate from lung cancer in this analysis was 0–65 per thousand in the test group and 0–6 per thousand in the control.[30]

The latest randomized clinical trial (RCT) regarding lung radiography screening known as the Prostate, Lung, Colorectal and Ovarian study (PLCO) was performed to prevent statistical flaws in RCTs supported by National Cancer Institute (NCI). A total of 155,000 men and women between 55–74 years of age in 10 centers were randomized for annual screening with posteroanterior (PA) lung radiography vs. 4 years of standard healthcare. The maximum follow-up was 13 years in the study in which more than half of the participants were active or former smokers. Compliance to screening was moderate (83%) during the study (79% during the third year and 87% at baseline). The rate of performing lung radiography in the control group was 11% (statistical contamination) during the study. While no significant difference was found between the groups in terms of lung cancer incidence, more stage I cancers were identified in the screened group compared to controls (462 vs. 374). Although no data was reported in the study regarding all-cause mortality, the disease-specific lung cancer mortality was found to be similar among the groups (relative risk [RR], 0.99; 95% confidence interval [CI], 0.87–1.22; p=0.48).[31]

NLST study, conducted in 33 centers in the USA between 2002–2004, is a randomized controlled trial that enrolled more than 53,000 high-risk asymptomatic smokers or former smokers with a smoking history of at least 30 package years between 55–74 years of age, and compared annual screening with LDCT with lung radiography for 3 years. The study was conducted by the American College of Radiology Imaging Network (ACRIN).[6] NLST is the largest randomized controlled trial conducted on lung cancer screening in high-risk individuals. The preliminary results of the NLST study led to significant changes for lung cancer screening. In the US, NLST demonstrated that mortality from lung cancer provides 20% less risk in high-risk individuals undergoing annual thorax LDCT screening compared to the participants screened by standard lung radiography.[32] LDCT captured higher number of lung cancers in early and potentially more treatable stages and reduced the mortality of lung cancer in high-risk individuals. The NELSON study, which is the largest European randomized LCS trial designed for the hypothesis stating 25% reduction would be achieved in 10-year lung cancer mortality in high-risk individuals screened using LDCT compared to those not screened, was conducted in the Netherlands and Belgium in 2003.[19,20] The other targets of the study were to estimate the influence of lung cancer screening on health related quality of life and quitting smoking,

and lung cancer screening costs among the subgroups.[33] In this study, 15,792 male and female participants between 50–74 years of age with a history of >15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years or those who quitted smoking within less than 10 years were randomized to LDCT and standard care arms. At 10 years follow-up of the NELSON study, 2,503 (9.3%) of a total of 27,000 screenings were identified as "indefinite", 598 (2.2%) as positive, and 243 (0.9%) lung cancers were detected. The PPD (Positive Predictive) value of the screening was calculated to be 41%. Approximately 50% of the cancers in the screening arm were at early stage and 65 to 70% were Stage IA to II, while nearly 70% of the cancers in the control arm were Stage III/IV at the time of diagnosis.[19] The NELSON trial showed that Volume CT screening enabled a significant reduction of harms (e.g., false positive tests and unnecessary workup procedures), without jeopardizing favorable outcomes.[19]

LDCT protocol have been used in various cost-effectiveness analyses in the last years in which LCS using LDCT appears cost-effective compared to no screening.[34–39] In a recent UK study, cost-effectiveness of LDCT screening versus no screening was evaluated, based on the NELSON study outcomes, resulting in an ICER of £5,455 per QALY. All analyses remained within the threshold of £20,000 per QALY, a commonly used WTP in the UK, showing that LCS with LDCT for a high-risk asymptomatic population is cost-effective in the UK.[40]

Several LCS initiatives have been presented in the recent years.[19,20] Croatia becomes the first European Union country that introduces nationwide screening for early lung cancer detection.[41] The European lung cancer screening trial: 4-IN-THE-LUNG-RUN (4ITLR), which is funded by European Commission and based on the NELSON results intents to include 26,000 participants at high-risk of lung cancer, in screening sites in the Netherlands, Germany, Spain, Italy and France aims to evaluate personalized strategies in recruitment, screening intervals, smoking cessation and other comorbidity preventing strategies.[33] Moreover, the European Respiratory Society (ERS) has recently published an open letter urging the European Union to take into account the importance of lung cancer early diagnosis and to extend the cancer screening to lung cancer.[42]

CONCLUSION

In conclusion, based on the results for cost per QALY and cost per LYG, implementation of the national lung cancer screening program was found very cost effective compared to the threshold identified for Türkiye. LYG by early screening as well as the benefits achieved by treating cancers identified in the early stage and the favorable outcomes in the quality of life both demonstrate that inclusion of lung cancer into routine screening programs in Türkiye will be an important achievement. The motto popularized by the Ministry of Health all over the country is "early diagnosis saves lives".

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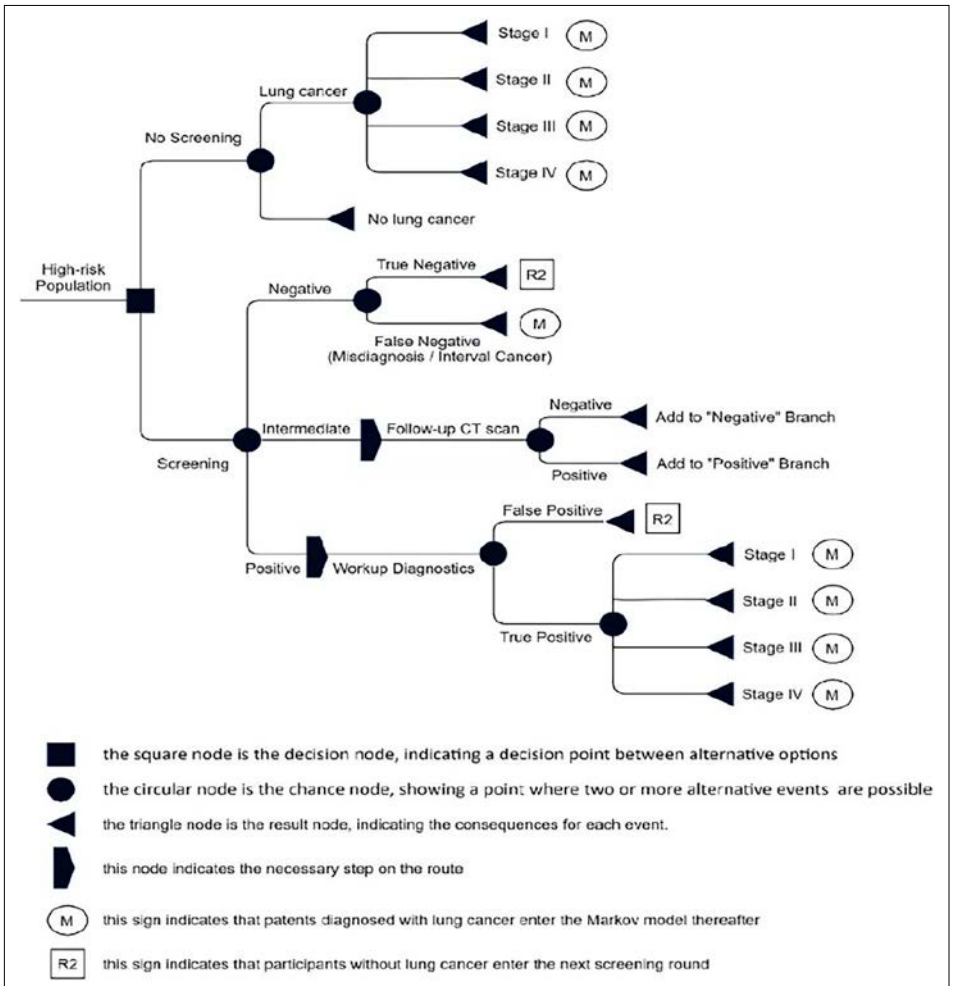
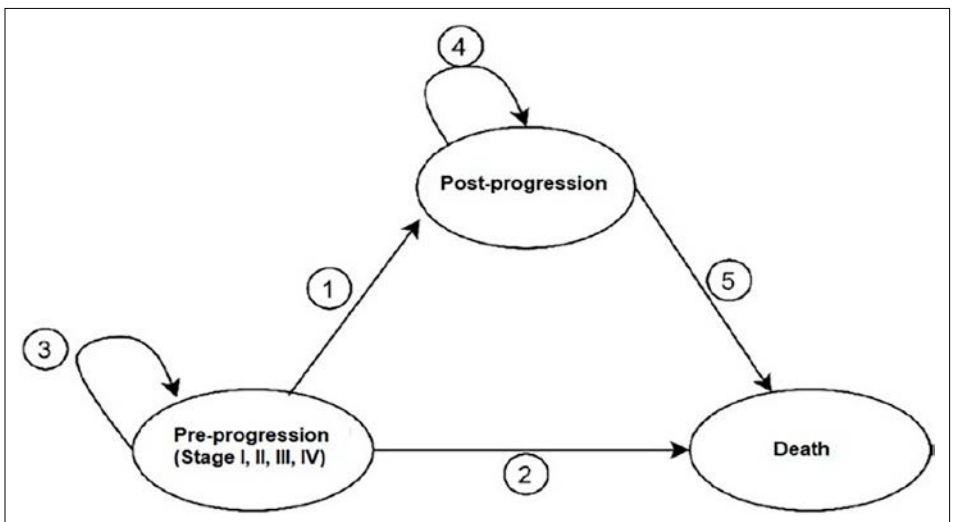


Appendix 1. Decision tree for lung cancer screening with the low-dose computed tomography.
CT: Computed tomography.



Appendix 2. Model structure for Markov Trace.