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Research Article

Early-stage lung cancer detection via thin-section low-dose CT reconstruction combined with AI in non-high risk populations: a large-scale real-world retrospective cohort study

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Abstract

Background: Current lung cancer screening guidelines recommend annual low-dose computed tomography (LDCT) for high-risk individuals. However, the effectiveness of LDCT in non-high-risk individuals remains inadequately explored. With the incidence of lung cancer steadily increasing among non-high-risk individuals, this study aims to assess the risk of lung cancer in non-high-risk individuals and evaluate the potential of thin-section LDCT reconstruction combined with artificial intelligence (LDCT-TRAI) as a screening tool.

Methods: A real-world cohort study on lung cancer screening was conducted at the West China Hospital of Sichuan University from January 2010 to July 2021. Participants were screened using either LDCT-TRAI or traditional thick-section LDCT without AI (traditional LDCT) . The AI system employed was the uAI-ChestCare software. Lung cancer diagnoses were confirmed through pathological examination.

Results: Among the 259 121 enrolled non-high-risk participants, 87 260 (33.7%) had positive screening results. Within 1 year, 728 (0.3%) participants were diagnosed with lung cancer, of whom 87.1% (634/728) were never-smokers, and 92.7% (675/728) presented with stage I disease. Compared with traditional LDCT, LDCT-TRAI demonstrated a higher lung cancer detection rate (0.3% vs. 0.2%, $P < 0.001$), particularly for stage I cancers (94.4% vs. 83.2%, $P < 0.001$), and was associated with improved survival outcomes (5-year overall survival rate: 95.4% vs. 81.3%, $P < 0.0001$).

Conclusion: These findings highlight the importance of expanding lung cancer screening to non-high-risk populations, especially never-smokers. LDCT-TRAI outperformed traditional LDCT in detecting early-stage cancers and improving survival outcomes, underscoring its potential as a more effective screening tool for early lung cancer detection in this population .

Keywords: lung cancer; non-high risk; low-dose computerized tomography; thin-section; artificial intelligence

Introduction

Lung cancer remains one of the most prevalent malignancies and the leading cause of cancer-related mortality globally. According to the GLOBOCAN 2022 report, an estimated 2.48 million new lung cancer cases and 1.81 million lung cancer-related deaths occurred worldwide in 2022, accounting for 12.4% of the total cancer diagnoses and 18.7% of all cancer-related deaths [1]. Notably, over one-third of these new cases and associated fatalities were reported in

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China [1]. A significant proportion of lung cancer cases are diagnosed at advanced stages, when curative surgical intervention is no longer feasible, leading to poor survival prognosis for patients [2]. These findings underscore the critical need for early detection strategies to improve prognosis and reduce the global burden of lung cancer.

Evidence demonstrates that low-dose computed tomography (LDCT) screening is an effective strategy for reducing lung cancer mortality by increasing the detection of early-stage disease [3–7]. Landmark randomized controlled trials (RCTs), such as the US National Lung Screening Trial (NLST) and the Dutch–Belgian Lung Cancer Screening Trial (NELSON), reported significant reductions in lung cancer mortality of 20% and 24%, respectively, with LDCT screening [3, 4]. Additionally, the Early Lung Cancer Action Project (ELCAP) revealed that LDCT screening can identify 85% of lung cancers at stage I, with a 10-year overall survival (OS) rate of 92% following surgical resection [5]. These pivotal findings have informed the development of evidence-based health policies for LDCT screening as a critical tool to mitigate the global burden of lung cancer.

LDCT screening is widely regarded as most effective for individuals at high risk of lung cancer [3, 4, 7]. For instance, the NLST targeted high-risk individuals aged 55–74 years with a smoking history of ≥30 pack-years, including those who had quit smoking within the past 15 years [3]. Current lung cancer screening guidelines in many countries primarily focus on tobacco exposure and age as key risk factors for determining eligibility [8–10]. However, it remains uncertain whether individuals outside this high-risk range, namely the non-high-risk population, can also benefit from LDCT screening. More importantly, recent studies have demonstrated that LDCT screening could detect a significant proportion of invasive lung cancers among never-smokers, highlighting the potential value of extending screening efforts to this population [11, 12]. Thus, additional studies are needed to improve risk evaluation standards and enhance the efficiency of LDCT screening in varied demographic groups.

Artificial intelligence (AI) has the potential to significantly enhance various aspects of lung cancer screening, such as lung nodule detection, nodule characterization, and the determination of personalized screening intervals [13–16]. To this end, we have developed DeepLN, a web-based semi-automatic annotation system powered by deep learning, which achieves an impressive nodule detection accuracy of 99.02% on CT screening images [17]. Additionally, our research suggests that AI can create innovative tools to improve early diagnosis and precision treatment for lung cancer and other major respiratory diseases [18–20]. However, it remains unclear whether individuals not classified as high-risk can benefit from LDCT screening programs integrated with AI technologies.

Herein, we performed a real-world cohort study involving 259 121 participants who underwent lung cancer screening with LDCT in the West China Hospital, Sichuan University. The aim of this study was to assess the risk of lung cancer in a non-high-risk population and evaluate the potential of thin-section LDCT reconstruction combined with AI (LDCT-TRAI) as a lung cancer screening tool.

Methods

Ethics committee approval and informed consent

This study was approved by the Ethics Committee of the West China Hospital, Sichuan University (No. 2019 [195]). All eligible participants provided written informed consent prior to their inclusion in the study.

Study design and participants

This study was a single-center, real-world retrospective cohort analysis of individuals who underwent LDCT for lung cancer screening at the West China Hospital, Sichuan University, between January 2010 and July 2021. In this study, the study population consisted of individuals classified as non-high risk based on the National Comprehensive Cancer Network (NCCN) guideline [8]. High-risk individuals were defined as those aged 55 to 77 years with a smoking history of ≥30 pack-years, who either currently smoke or, if a former smoker, had quit within the past 15 years [8]. Participants who did not meet these high-risk criteria were categorized as non-high-risk individuals. In addition, eligible non-high-risk participants had not undergone any chest imaging examinations within the 18 months prior to enrollment, and reported no new or aggravated respiratory symptoms such as cough, expectoration, chest tightness, hemoptysis, and dyspnea. Exclusion criteria included: (i) prior diagnosis of unknown or malignant lung nodules, masses, atelectasis, or enlarged hilum; (ii) history of lung cancer; (iii) history of partial or total lobectomy; (iv) unknown smoking history; (v) unexplained weight loss of >5 kg in the past year; and (vi) high-risk individuals.

The enrolled study population was further stratified into two groups according to the LDCT screening protocol: the LDCT-TRAI group (undergoing LDCT combined with an AI-assisted procedure) and the traditional LDCT group (undergoing traditional thick-section LDCT without AI integration).

Participants were categorized into smokers and never-smokers based on their smoking status. Never-smokers were defined as individuals who had either never smoked or had smoked <100 cigarettes in their lifetime [21]. Demographic data and clinical information, including medical history and smoking status (duration of smoking, pack-years, and duration of smoking cessation for former smokers), were collected by internally trained physicians following standardized training. Individuals who did not provide clear or complete information regarding their smoking status were excluded from the study.

Procedures

All enrolled non-high-risk participants underwent lung cancer screening using either thin-section LDCT reconstruction or traditional LDCT. The LDCT scans were performed using a dual-row spiral CT scanner (Somatom Emotion Duo, Siemens, Germany). A low-dose protocol was employed for all scans, with settings of 120 kVp, 16 (20 mA/0.8 s) to 40 (50 mA/0.8 s) mAs, a pitch of ≤1 cm, and a rotation time of 0.8 s. All equipment used for screening adhered to established technical standards [3, 18]. Traditional thick-section LDCT images were reconstructed with a slice thickness of 5 mm, while thin-section LDCT images were reconstructed with a slice thickness of 1 mm.

The thin-section LDCT images in DICOM format were processed using the uAI-ChestCare software (version 0430; Shanghai United Imaging Healthcare Co., Ltd.), which enabled image segmentation and extraction of texture features [22–24]. This AI software automatically delineated the complete 3D region of interest for identified lesions by outlining their boundaries on consecutive axial images of lung window (with a window level of −600 (hounsfield unit, HU) and a window width of 1 500 HU) [22]. Following this, the software computed various quantitative and texture features of the lung lesions, including location, nodule type, max-

imum diameter, solid volume, and entropy [22]. The identified lesions were subsequently reviewed and confirmed by experienced radiologists with a minimum of 5 years of expertise in chest radiology.

The traditional LDCT images were independently evaluated by two radiologists with at least 5 years of experience in chest radiology. In cases where their interpretations differed, the radiologists engaged in repeated analysis and discussion until a consensus was reached. All participating radiologists were certified by relevant agencies and underwent testing to ensure inter-rater reliability and intra-rater reliability.

Positive screening results were defined as: (i) any uncalcified nodule with a diameter ≥ 4 mm or (ii) other abnormalities such as obstructive atelectasis, soft tissue opacity, or patchy clouding opacity [3]. In cases where multiple nodules were detected, the dominant nodule—defined as the largest and most suspicious nodule—was selected for further evaluation [8, 25]. We conducted a thorough review of the medical records of participants with positive results. Patients identified with lung nodules were referred to a pulmonologist in accordance with the NCCN guidelines for further follow-up or diagnostic procedures [8].

A professional follow-up team was responsible for ascertaining probable vital status of participants. Specialized training was provided to the follow-up personnel to ensure accurate data collection. These individuals were monitored for lung cancer events for a period of at least 1 year following their inclusion in the study. The follow-up deadline was 31 December 2023. OS was defined as the duration from the initial diagnosis of lung cancer to the date of death or 31 December 2023, whichever occurred first.

Outcome measure

The primary outcome of this study was the lung cancer detection rate, defined as the proportion of lung cancer cases identified among all screened non-high-risk participants. Secondary outcomes included the positive screening result rate, the proportion of stage I lung cancer cases, and the 5-year OS rate among diagnosed lung cancer patients.

Lung cancer was pathologically confirmed through image-guided aspiration or post-surgical biopsy. Participants with positive results and a high suspicion of lung cancer were recommended to undergo invasive diagnostic procedures in alignment with the NCCN guidelines [12]. Comprehensive data on diagnostic evaluation procedures for participants with highly suspicious results, including pathology reports, surgical records, and treatment details, were thoroughly reviewed. Histological classification of lung cancer was determined according to the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) [26]. Lung cancer staging was determined based on the eighth edition of the Cancer Staging Manual of the American Joint Committee on Cancer (AJCC) [27].

Statistical analysis

Statistical analyses were conducted using IBM SPSS 26.0. Continuous variables are expressed as mean ± standard deviation (SD) or median with the full range, while categorical variables are presented as frequencies and percentages. For comparisons between two groups, Student's *t* test was employed for continuous variables, and Pearson chi-square test or Fisher's exact test were used for categorical variables, as appropriate. Survival analysis was performed by the Kaplan–Meier method, with differences between survival curves assessed by the log-rank test. The hazard ratio (HR) of cancer development was estimated by Cox proportional hazard regression analysis, with adjustment for potential confounding variables, including age, sex, histologic type, history of lung disease, and nodule size. A two-sided *P* value < 0.05 was considered as statistically significant.

Results

Characteristics of the participants

A total of 273 832 participants underwent lung cancer screening with LDCT from January 2010 through July 2021. Of these, 9 053 participants who had previously been diagnosed with lung cancer or had an unknown smoking status, and 5 658 participants classified as high-risk individuals were excluded from the analysis (Fig. 1). Consequently, 259 121 non-high-risk participants were included in this study (Table 1). The mean age of the included participants was 44.7 years. The majority of participants (78.5%, 203 406/259 121) were never-smokers. The mean smoking volume of the included participants was 15.1 pack-years and the mean duration of smoking cessation was 5.1 years. Notably, 92.7% (240 205/259 121) of non-high-risk participants had no history of chronic lung disease, history of malignancy, or family history of lung cancer. Among the included participants, 196 069 (75.7%) received LDCT-TRAI screening, while 63 052 (24.3%) received traditional thick-section LDCT screening.

We have conducted statistical analysis on the variables between the LDCT-TRAI and traditional LDCT cohorts. The results showed that compared with the traditional LDCT cohort, the LDCT-TRAI cohort had more women (46.6% vs. 43.9%, $P < 0.001$), more young people <40 years old (39.5% vs. 27.6%, $P < 0.001$), more never-smokers (79.1% vs. 76.7%, $P < 0.001$), less smoking volume (14.8 pack-years vs. 16.1 pack-years, $P < 0.001$), shorter quitting time (4.6 years vs. 6.7 years, $P < 0.001$), and fewer chronic lung diseases (6.5% vs. 9.1%, $P < 0.001$).

Screening

Among all the non-high-risk participants, the rate of positive screening results and positive lung nodules were 33.7% (87 260/259 121) and 32.0% (82 833/259 121), respectively (Table 2). The mean diameter of the detected positive lung nodules was 6.61 mm. The overall lung cancer detection rate in the non-high-risk cohort was 0.3% (728/259 121; Table 2).

To evaluate the efficacy of LDCT-TRAI screening, we conducted a comparative analysis of the screening results between the LDCT-TRAI group and traditional LDCT group. The LDCT-TRAI program demonstrated a significantly higher detection rate of positive results (35.3% vs. 28.6%, $P < 0.001$), positive nodules (34.1% vs. 25.4%, $P < 0.001$), and small positive nodules with diameter of 4–10 mm (91.2% vs. 88.2%, $P < 0.001$) compared to the traditional LDCT group (Table 2). Additionally, the LDCT-TRAI program identified a higher lung cancer detection rate (0.3% vs. 0.2%, $P < 0.001$). The overall missed follow-up rate was 0.4%.

Characteristics of lung cancer

Detailed characteristics of lung cancers identified in non-high-risk participants are described in supplementary Table 1, see online supplementary material. The majority of lung cancer cases were female, comprising 64.7% of the cohort. In terms of age distribution, 59.3% of patients were aged ≥50 years, 25.0% were between 40 and 49 years, and 15.7% were <40 years of age. Most lung cancer patients (87.1%) were never-smokers. Notably, among patients aged ≤49 years, 91.2% were never-smokers.

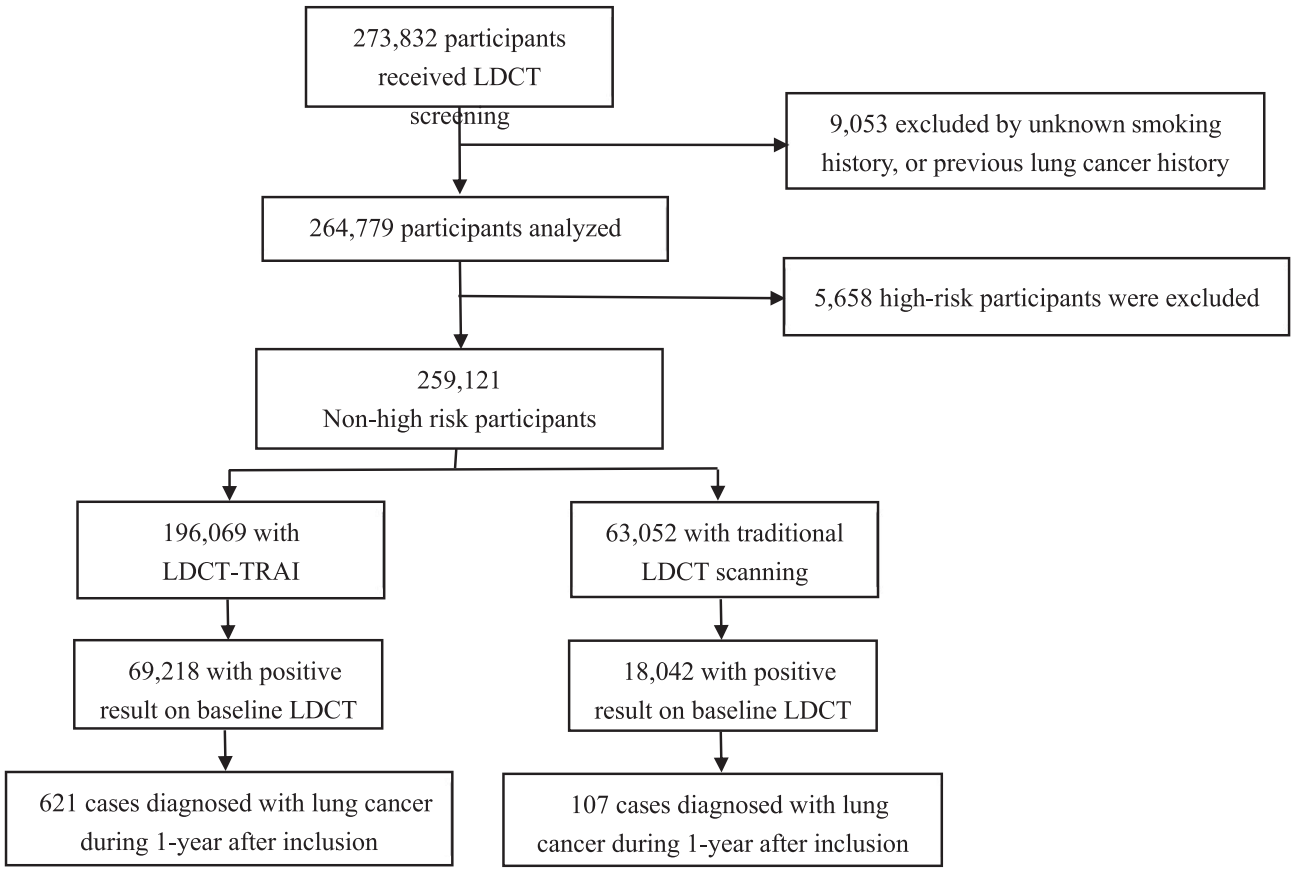

Figure 1. Flowchart of the participant selection process. High-risk participants are individuals aged 55 to 77 years with a ≥30 pack-year history of smoking tobacco who currently smoke or, if former smoker, have quit within 15 years.

Even for those who did smoke, 59·6% had a smoking history of <20 pack-years. Of the patients who had quit smoking, 64.7% had ceased smoking for <5 years. History of chronic lung disease (10.2%), history of malignancy (1.5%), and family history of lung cancer (4.3%) were relatively uncommon among lung cancer patients (supplementary Table 1). Regarding tumor characteristics, ground-glass nodule type lung cancers were the most prevalent, accounting for 42.6% of cases, followed by partial solid lung cancers (38.7%), and solid lung cancers (18.7%; Supplementary Table 1).

Stages and histologic types of lung cancers

Among the lung cancers detected in non-high-risk participants, 93.8% were diagnosed at stage 0 or I, with only 3.0% identified at stage IV (Table 3). The majority of these lung cancers (84.5%) were adenocarcinoma. Compared with lung cancer of ever-smokers, never-smokers with lung cancer had more adenocarcinoma (87.1% vs. 67.1%, $P < 0.001$) and less squamous cell carcinoma (0.9% vs. 9.6%, $P < 0.001$).

Additionally, the LDCT-TRAI program demonstrated a significant tendency to detect lung cancers at earlier stages compared to traditional LDCT scanning, with 94.4% of cases detected at stage I by LDCT-TRAI vs. 83.2% by traditional LDCT, ($P < 0.001$; Table 3). Notably, stage IA1 lung cancers accounted for 46.9% in those detected by LDCT-TRAI, a proportion significantly higher than the 25.2% detected by traditional LDCT scanning ($P < 0.001$; Table 3).

Survival

Among non-high-risk participants, 728 cases were diagnosed with lung cancer within 1 year of inclusion. The median follow-up periods for these patients was 4.25 years (range 0.02–11.51 years). During this period, 46 deaths (6.3%) were recorded among the 728 cases. The estimated 5-year OS rate among non-high-risk participants with lung cancer was 91.8%. The missed follow-up rate was 4.8%.

We conducted a comparative analysis on lung cancer patients between the LDCT-TRAI group and the traditional LDCT group. The estimated 5-year OS rate for lung cancer patients diagnosed by LDCT-TRAI was 95.4%, compared to 81.3% for those diagnosed by traditional LDCT scanning. Kaplan–Meier survival estimates with the log-rank test demonstrated that patients diagnosed through LDCT-TRAI had significantly better survival outcomes than those diagnosed by traditional LDCT ($P < 0.0001$; Fig. 2). In the Cox proportional HR analysis adjusted for age, sex, histologic type, lung disease history, and nodule size, traditional LDCT was associated with a higher risk of mortality compared to LDCT-TRAI [HR = 4.334, 95% confidence interval (CI): 1.758–10.684; Table 4].

Discussion

We conducted a large descriptive cohort study to investigate the effectiveness of LDCT screening combined with AI technology in reducing the burden of lung cancer among non-high-risk individuals. Among 259 121 eligible participants, lung cancer was detected in 0.3% of the non-high-risk participants through LDCT

Table 1. Selected baseline characteristics of the study participants.

Characteristic	Total (n = 259 121)	LDCT-TRAI (n = 196 069)	Traditional LDCT (n = 63 052)	P value
Sex, n (%)				
Male	140 044 (54.0)	104 650 (53.4)	35 394 (56.1)	< 0.001
Female	119 077 (46.0)	91 419 (46.6)	27 658 (43.9)	< 0.001
Age at inclusion (years), n (%)	44.66 ± 12.67	43.95 ± 12.55	46.87 ± 12.81	< 0.001
< 40	94 747 (36.6)	77 375 (39.5)	17 372 (27.6)	< 0.001
40–49	79 623 (30.7)	57 012 (29.1)	22 611 (35.9)	< 0.001
50–59	53 315 (20.6)	39 972 (20.4)	13 343 (21.2)	< 0.001
60–69	20 607 (8.0)	14 821 (7.6)	5786 (9.2)	< 0.001
70–79	8052 (3.1)	5204 (2.7)	2848 (4.5)	< 0.001
≥ 80	2777 (1.1)	1685 (0.9)	1092 (1.7)	< 0.001
Smoking status, n (%)				
Ever-smoking	55 715 (21.5)	41 039 (20.9)	14 676 (23.3)	< 0.001
Never-smoking	203 406 (78.5)	155 030 (79.1)	48 376 (76.7)	< 0.001
Smoking volume (pack-years), n (%)	15.10 ± 11.62	14.75 ± 11.48	16.09 ± 11.95	< 0.001
< 20	35 791 (64.2)	26 967 (65.7)	8824 (60.1)	< 0.001
20–29	12 762 (22.9)	9006 (21.9)	3756 (25.6)	< 0.001
≥ 30	7162 (12.9)	5066 (12.3)	2096 (14.3)	< 0.001
Quit smoking (years), n (%)	5.10 ± 6.72	4.55 ± 5.87	6.70 ± 8.55	< 0.001
< 5	3250 (65.6)	2509 (67.9)	741 (58.9)	< 0.001
5–14	1217 (24.6)	905 (24.5)	312 (24.8)	0.822
≥ 15	487 (9.8)	282 (7.6)	205 (16.3)	< 0.001
Chronic lung disease[a], n (%)				
Yes	18 416 (7.1)	12 672 (6.5)	5744 (9.1)	< 0.001
No	240 705 (92.9)	183 397 (93.5)	57 308 (90.9)	< 0.001
History of malignancy, n (%)				
Yes	2579 (1.0)	1994 (1.0)	585 (0.9)	0.050
No	256 542 (99.0)	194 075 (99.0)	62 467 (99.1)	0.050
Family history of lung cancer, n (%)				
Yes	7386 (2.9)	5570 (2.8)	1816 (2.9)	0.606
No	251 735 (97.1)	190 499 (97.2)	61 236 (97.1)	0.606

[a]Chronic lung diseases include chronic obstructive pulmonary disease, diffuse pulmonary fibrosis, history of pulmonary tuberculosis, chronic bronchitis, emphysema, and bronchiectasis.

Table 2. Comparison of LDCT-TRAI and traditional LDCT screening.

Characteristic	Total	LDCT-TRAI	Traditional LDCT	P value
Total no. screened, n (%)	259 121	196 096	63 052	
Positive result, n (%)	87 260 (33.7)	69 218 (35.3)	18 042 (28.6)	< 0.001
Negative result, n (%)	171 861 (66.3)	126 851(64.7)	45 010 (71.4)	< 0.001
Positive lung nodule, n (%)	82 833 (32.0)	66 838 (34.1)	15 995 (25.4)	< 0.001
Size (mm), n (%)	6.61 ± 3.54	6.50 ± 3.44	7.09 ± 3.88	< 0.001
4–10	75 090 (90.7)	60 980 (91.2)	14 110 (88.2)	< 0.001
11–20	6501 (7.8)	4952 (7.4)	1549 (9.7)	0.338
21–30	1242 (1.5)	906 (1.4)	336 (2.1)	0.025
Lung cancer confirmed	728 (0.3)	621 (0.3)	107 (0.2)	< 0.001

screening. Our results highlight that the LDCT-TRAI strategy was associated with a higher detection rate of early-stage lung cancer and improved survival outcomes in non-high-risk individuals. To our knowledge, this represents the largest real-world study to date evaluating the efficacy of the LDCT-TRAI strategy for early lung cancer detection in non-high-risk individuals. This study underscores the potential of integrating LDCT with AI as a precision medicine approach, enabling more accurate early detection of lung cancer in non-high-risk populations. By identifying early-stage cancers that might otherwise go undiagnosed, this strategy aligns with the goals of precision medicine, aiming to improve patients' prognosis and reduce unnecessary healthcare burdens.

To optimize lung cancer screening programs, greater emphasis should be placed on precisely identifying eligible participants, especially among individuals currently classified as non-high risk. In our study, LDCT screening detected a significant number of lung cancers in the non-high-risk participants, with a detection rate of 0.3%. This finding aligns with a prospective cohort study in China, which reported a lung cancer detection rate of 0.2% among never-smoker participants undergoing LDCT screening [28]. Similarly, a Korean study demonstrated a lung cancer detection rate of 0.45% among 12 176 never-smokers who underwent LDCT screening [12]. Furthermore, our results revealed that the majority of lung cancers detected in the non-high-risk group were diagnosed at an

Table 3. Stages and histologic types of lung cancers.

Characteristic	Total (*n* = 728)	LDCT-TRAI (*n* = 621)	Traditional LDCT (*n* = 107)	P value
Stage, *n* (%)				
0[a]	8 (1.1)	4 (0.6)	4 (3.7)	0.019
I	675 (92.7)	586 (94.4)	89 (83.2)	< 0.001
IA1	318 (43.7)	291 (46.9)	27 (25.2)	< 0.001
IA2	257 (35.3)	215 (34.6)	42 (39.3)	0.355
IA3	74 (10.2)	58 (9.3)	16 (15.0)	0.076
IB	26 (3.6)	22 (3.5)	4 (3.7)	0.784
II	6 (0.8)	6 (1.0)	0 (0.0)	0.600
III	17 (2.3)	12 (1.9)	5 (4.7)	0.083
IV	22 (3.0)	13 (2.1)	9 (8.4)	< 0.001
Histologic type, *n* (%)				
Adenocarcinoma	615 (84.5)	528 (85.0)	87 (81.3)	0.327
Adenocarcinoma *in situ*	24 (3.3)	14 (2.3)	10 (9.3)	< 0.001
Minimally invasive adenocarcinoma	5 (0.7)	5 (0.8)	0 (0.0)	1.000
Invasive adenocarcinoma	586 (80.5)	509 (82.0)	77 (72.0)	0.016
Squamous cell carcinoma	15 (2.1)	12 (1.9)	3 (2.8)	0.473
SCLC[b]	9 (1.2)	5 (0.8)	4 (3.7)	0.031
Large cell lung cancer	1 (0.1)	1 (0.2)	0 (0.0)	1.000
Other NSCLC[b]	88 (12.1)	75 (12.1)	13 (12.1)	0.983

[a]Carcinoma *in situ* formerly referred to as bronchioloalveolar cell carcinoma. [b]SCLC, small-cell lung cancer; NSCLC, non-small cell lung cancer.

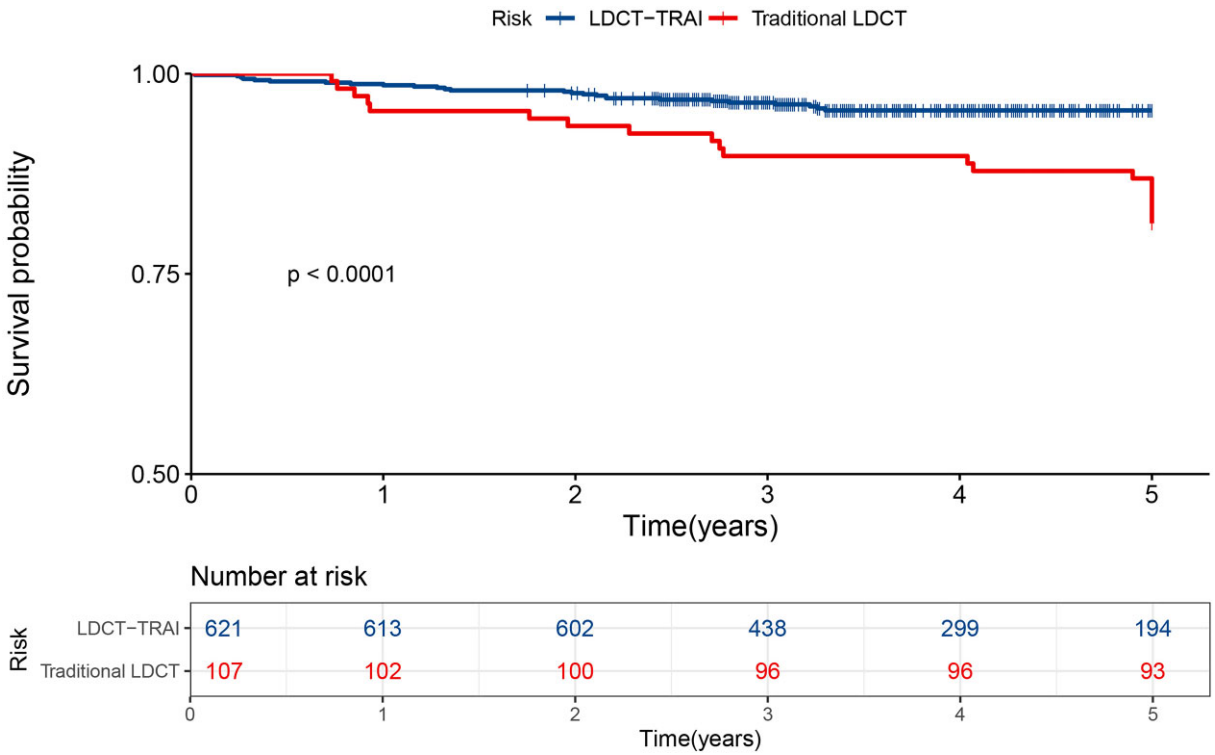

Figure 2. Survival curves of patients with lung cancer diagnosed by LDCT-TRAI and traditional LDCT scanning.

Table 4. Adjusted HR (aHR) of lung cancer mortality adjusted by Cox porpotional hazard regression.

Category	aHR	95% CI	*P* value
By LDCT procedure[a]			
LDCT-TRAI	1		
Traditional LDCT	4.334	1.758–10.684	0.00 145

[a]Adjusted by age, sex, histologic type, lung disease history, and nodule size.

early stage, with 92.7% identified at stage I. This is consistent with findings from a previous Korean study that reported that 92.7% of lung cancers detected via LDCT screening in never-smokers were at stage 0 or I [12].

In the non-high-risk population, particular emphasis should be placed on never-smoker individuals, as they constitute a significant proportion of lung cancer cases. In our study, 87.1% of lung cancer patients in the non-high-risk group were never-smokers,

and 84.5% had adenocarcinomas. In never-smokers with lung cancer, 87.1% had adenocarcinomas, which was higher than for ever-smokers with lung cancer. This was similar to a study in Korea, which found that never-smokers with lung cancer had more adenocarcinoma and less squamous cell carcinoma compared with ever-smokers with lung cancer [12]. While smoking remains a major risk factor for lung cancer, recent epidemiological data have demonstrated a rising incidence of lung cancer in never-smokers (LCINS) over the past few decades, particularly in Asian countries [29–33]. LCINS is estimated to have been the fifth leading cause of cancer-related deaths worldwide in 2023 [33]. In China and other Asian nations, never-smokers account for 31%–48% of all lung cancer cases [29–31]. This upward trend may be partly attributed to the success of smoking cessation interventions, which have led to a reduction in smoking-related lung cancer incidence [34, 35]. More importantly, environmental factors such as air pollutants (e.g. PM2.5), germline mutations in susceptibility genes, and other genetic and environmental determinants have been implicated in the increased incidence of LCINS [36–39]. Future research must focus on identifying high-risk individuals for lung cancer within the never-smoker population to develop precise and personalized screening strategies.

Globally, a notable increase in both the number and proportion of relatively younger lung cancer patients has been observed [29, 40, 41]. However, the optimal age for initiating lung cancer screening remains uncertain, as screening guidelines vary widely across different countries [9, 10, 15]. In our study, while more than half of the patients (59.3%) were aged ≥ 50 years, a substantial proportion (25.0%) were between 40 and 49 years of age. Notably, among patients aged 40 to 49 years, 87.9% were never-smokers. This observation aligns with the findings of Li *et al.*, who analyzed data from 26 lung cancer LDCT screening studies involving 117 586 participants worldwide [42]. Their analysis revealed that although the overall detection rate of lung cancer increased with age, the detection rate of early-stage lung cancer exhibited an inverse trend, declining with advancing age. Specifically, initiating screening at the age of 40 years was associated with a higher proportion of early-stage lung cancer detection compared to initiating screening at 50 or 55 years of age. Based on our findings and the evidence from previous studies, it is recommended that LDCT screening for lung cancer should commence at the age of 40 years or above.

When exploring the value of AI in lung cancer screening with LDCT, we discovered that integrating thin-section LDCT with AI significantly enhances screening efficiency for early lung cancer detection. While prior studies have established AI's role in nodule detection and distinguishing between benign and malignant pulmonary nodules [13, 17, 43], our study is the first to specifically evaluate the effectiveness of AI in LDCT screening within a non-high-risk population. Our findings demonstrate that LDCT-TRAI identified more positive results, positive lung nodules, and small nodules (4–10 mm) compared to traditional LDCT. Additionally, the integration of thin-section LDCT and AI detected a higher number of stage I lung cancers, particularly stage IA1, while reducing the number of stage IV cases. Specifically, LDCT-TRAI increased the detection rate of stage I lung cancer by 11.9% compared to traditional LDCT. Most importantly, the use of LDCT-TRAI was associated with a significantly improved survival benefit for lung cancer patients, with a 5-year OS rate of 95.4% vs. 81.3% for those detected by traditional LDCT ($P = 0.003$). These results underscore that LDCT-TRAI offers a substantially higher detection rate and survival benefit for non-high-risk populations, highlighting its potential to transform early lung cancer screening.

Several limitations of this study should be acknowledged. First, it was not a prospective RCT but rather a retrospective cohort study conducted at a single center, which may introduce selection bias and limit the generalizability of the findings. To address this limitation, we are planning a multicenter prospective RCT to further evaluate the efficacy of LDCT combined with AI strategy in detecting early-stage lung cancer among non-high-risk populations. Second, although participants with positive results highly suggestive of lung cancer were recommended to undergo invasive diagnostic procedures following NCCN guidelines, variability in adherence to these recommendations may have influenced the accuracy of our outcomes. Third, all participants in this study were from China, which means the results may be influenced by marked racial and ethnic differences.

In conclusion, this real-world cohort study represents the first large-scale investigation into lung cancer screening among non-high-risk populations in China. Our findings reveal a substantial number of lung cancer cases among individuals not traditionally considered high-risk, for whom LDCT screening is not currently recommended. This underscores the need for increased attention to lung cancer screening in non-high-risk populations, particularly among never-smokers. The use of thin-section LDCT combined with AI demonstrated superior efficacy in detecting early-stage lung cancer and improving survival outcomes compared to traditional LDCT in this population. These results provide compelling evidence to inform and optimize future lung cancer screening guidelines.

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Supplementary data

Supplementary data are available at *PCMEDI* online.

Conflict of interest

None declared. In addition, as a co-Editor-in-Chief of *Precision Clinical Medicine*, the corresponding author Weimin Li was blinded from reviewing and making decisions on this manuscript.

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