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HUNCHEST-II contributes to a shift to earlier-stage lung cancer detection: final results of a nationwide screening program

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Abstract

Objectives The introduction of low-dose CT (LDCT) altered the landscape of lung cancer (LC) screening and contributed to the reduction of mortality rates worldwide. Here we report the final results of HUNCHEST-II, the largest population-based LDCT screening program in Hungary, including the screening and diagnostic outcomes, and the characteristics of the LC cases.

Methods A total of 4215 high-risk individuals aged between 50 and 75 years with a smoking history of at least 25 pack-years were assigned to undergo LDCT screening. Screening outcomes were determined based on the volume, growth, and volume doubling time of pulmonary nodules or masses. The clinical stage distribution of screen-detected cancers was compared with two independent practice-based databases consisting of unscreened LC patients.

Results The percentage of negative and indeterminate tests at baseline were 74.2% and 21.7%, respectively, whereas the prevalence of positive LDCT results was 4.1%. Overall, 76 LC patients were diagnosed throughout the screening rounds (1.8% of total participants), out of which 62 (1.5%) patients were already identified in the first screening round. The overall positive predictive value of a positive test was 58%. Most screen-detected malignancies were stage I LCs (60.7%), and only 16.4% of all cases could be classified as stage IV disease. The percentage of early-stage malignancies

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was significantly higher among HUNCHEST-II screen-detected individuals than among the LC patients in the National Koranyi Institute of Pulmonology's archive or the Hungarian Cancer Registry ($p < 0.001$).

Conclusions HUNCHEST-II demonstrates that LDCT screening for LC facilitates early diagnosis, thus arguing in favor of introducing systematic LC screening in Hungary.

Clinical relevance statement HUNCHEST-II is the so-far largest population-based low-dose CT screening program in Hungary. A positive test's overall positive predictive value was 58%, and most screen-detected malignancies were early-stage lesions. These results pave the way for expansive systematic screening in the region.

Key Points

- *Conducted in 18 medical facilities, HUNCHEST-II is the so far largest population-based low-dose CT screening program in Hungary.*
- *The vast majority of screen-detected malignancies were early-stage lung cancers, and the overall positive predictive value of a positive test was 58%.*
- *HUNCHEST-II facilitates early diagnosis, thus arguing in favor of introducing systematic lung cancer screening in Hungary.*

Keywords Lung cancer, Low-dose computed tomography screening, Early detection

Introduction

Lung cancer (LC) is one of the most frequently diagnosed cancers worldwide and the leading cause of cancer-related deaths in both genders [1]. If identified at an early stage, surgical resection offers a favorable prognosis [2, 3]. In addition, the opportunity for improving survival with systemic therapy is also more pronounced at earlier disease stages [4]. Nevertheless, owing to the absence of evident clinical symptoms, most patients already have distant metastases at the time of initial diagnosis, when treatment options are limited [5]. Thus, in order to maximize the impact of therapeutic interventions (surgery and systemic therapy) and to increase survival outcomes, it is crucial to detect LC as early as possible.

Advances in low-dose CT (LDCT) imaging have made the detection of lung nodules possible at acceptable levels of radiation exposure, even when they are indetectable for chest radiography [6, 7]. In the U.S.-based National Lung Screening Trial (NLST), more than 50,000 high-risk individuals were randomly assigned to screening with periodic LDCT or chest radiographs over 3 years [8]. Importantly, although showing an apparent reduction in both LC-related and overall mortality among participants who underwent LDCT screening (20% and 6.7%, respectively), NLST had a concerningly high false positivity rate (96.4%) [8]. To overcome this latter issue, the NELSON study, one of Europe's most extensive screening trials, adopted a modified screening protocol with three different screening outcomes [9, 10]. Moreover, screening results were primarily based on volume and volume-doubling time (VDT) rather than the diameter solely [9]. With these revised evaluation protocols, the NELSON trial showed a significant reduction in LC mortality with an acceptable false positivity rate [9, 10]. Since then, several population-based screening programs have demonstrated the beneficial effects of LDCT screening in finding surgically treatable LC cases and reducing mortality [11–14]. In view of these results, many scientific societies now recommend LDCT-based LC screening for all high-risk individuals [5].

Hungary has been reported to have one of the highest LC mortality rates worldwide (69.7 and 29.3 per 100,000 person-years in men and women, respectively), thus highlighting the need for implementing a large-scale screening program [15, 16]. Therefore, in 2014, the Hungarian LDCT LC pilot screening program (HUNCHEST) was initiated to evaluate the feasibility of a nationwide screening program in Hungary [17, 18]. By performing regular LDCT scans on 1890 participants, HUNCHEST revealed that the used nodule-management protocol could be applied in real-life scenario and demonstrated that LDCT indeed constitutes a powerful tool for early diagnosis [17]. Specifically, HUNCHEST had an overall positive predictive value (PPV) of 31.6%, and most lung malignancies were diagnosed at an early stage [17]. Here we report the final results of the subsequent HUNCHEST-II, the largest population-based LDCT screening program in Hungary, including the screening outcomes, the results of the diagnostic evaluation, and the characteristics of the LC cases.

Participants and methods

Study design

HUNCHEST-II was a prospective, multicenter, single-arm screening study conducted in 18 medical centers across Hungary. The list of participating institutes is shown in Supplementary Table 1. The national-level ethics committee (Hungarian Scientific and Research Ethics Committee of the Medical Research Council, approval number: ETT-TUKEB, 002524–005/2014/OTIG) and the local medical board of each participating site approved

the study. Written informed consent was obtained from all study participants. The primary aim of HUNCHEST-II was to evaluate the efficiency of LDCT in LC detection in an asymptomatic high-risk population by determining the incidence of solitary pulmonary nodules and LC among participants. The secondary objective was to assess the impact of LDCT screening on early detection. In addition, the modeling of patient pathways after positive screening was also assessed. However, due to the COVID-19 pandemic, the analysis thereof was not statistically viable.

Recruitment

Recruitment processes were undertaken independently at each participating center between September 9, 2019, and January 1, 2022. Details concerning the recruitment methods and eligibility criteria are further described in Supplementary Methods.

LDCT screening

For CT screening, LDCT scans were obtained by machines already available at the institutions that reached the requirement of at least 64 slices, and which could perform the low-dose protocol as explained below. Following the recommendations of the UK Lung Cancer Screening Trial [19], all screening sites were required to have daily quality control assurance for the CT scanners, using a water and body phantom. LDCT images performed craniocaudally from lung apices to bases were obtained during suspended maximal inspiration in a single breath-hold with a low-dose setting (120 kV, 20 mAs) and were reconstructed in overlapping contiguous 1- and 5-mm increments. During the scanning, the average $CTDI_{vol}$ was ≈1.5 mGy, while the effective radiation dose was kept under 3 mSv. Data acquisition protocols and screening conditions were standardized across participating institutions. Radiological analyses and subsequent interpretations were performed as described in the HUNCHEST pilot study [17]. All images were interpreted by board-certified radiologists with > 5 years of experience in thoracic imaging and were also analyzed by the Veye lung nodules software (Supplementary Methods). Of note, in HUNCHEST-II, the Veye Lung Nodules software was used only as a complementary tool to assist the radiologists rather than as a definitive diagnostic instrument. For standardization and quality check of radiological interpretation, representative images and teaching scans were discussed regularly among radiologists from different screening sites.

HUNCHEST-II nodule management protocol

The screening rounds and the detailed nodule-management protocol have been described previously in the HUNCHEST pilot study [17] and are briefly elaborated in Supplementary Methods. Of note, due to the COVID-19 pandemic, screening was completely halted between 15 March 2020 and 15 June 2020. Waiting lists between March 2020 and December 2021 were also considerably affected by the pandemic. Assessment of indeterminate or positive results was not affected; however, patient compliance was lower than usual.

Statistical analysis

All statistical analyses were performed with the use of GraphPad Prism Version 8 and SPSS Statistics 26.0 package (SPSS Inc.). See Supplementary Methods for details.

Results

Study population and baseline screening results

In the HUNCHEST-II screening program, 4215 high-risk individuals aged between 50 and 75 years were included (Table 1). Among them, 2254 (53.5%) and 1961 (46.5%) were women and men, respectively. The mean age at enrollment was 61.32 (95% CI 60.1 to 62.6) years, and current smokers were significantly younger than those who had quit smoking in the last 15 years ($p < 0.001$). Also, the percentage of current smokers was significantly higher among women compared to men (55.1% vs. 44.9%, respectively; $p < 0.001$). The occurrence of COPD did not differ according to smoking habits ($p = 0.524$).

The percentage of negative and indeterminate tests at baseline were 74.2% and 21.7%, respectively, whereas the prevalence of positive LDCT results was 4.1% (Table 2). The number of both positive and indeterminate screening results was notably higher in elderly participants (i.e., age ≥ 65) compared to those younger than 65 years of age ($p < 0.001$). Although most current smokers were women, no significant association was found between gender and baseline screening results ($p = 0.078$). As expected, however, the presence of COPD considerably increased the probability of indeterminate and positive outcomes ($p < 0.001$). Specifically, the occurrence of positive screens at baseline was nearly double in people with COPD (6.1%) than in participants without this respiratory comorbidity (3.8%).

Outcomes of follow-up screening rounds

Figure 1 shows the participation flowchart of the HUNCHEST-II screening study within different screening rounds. In addition to the 174 individuals with positive screens at baseline, the suspicion for an eventual malignancy was raised in 31 participants in subsequent screening rounds, leading to a total of 205 positive cases (overall prevalence: 4.1%). The number of negative outcomes in the second and third screening round was 607 and 27, respectively. Notably, only eight individuals from the initial test-negative group had a positive

Table 1 Clinicopathological characteristics of the HUNCHEST II study participants

	Overall	Former smokers	Current smoker	*p* value[a]
All participants	4215	931	3284	
Age (years)	61.32 years 95% CI [60.1, 62.6]	63.10 years 95% CI [62.9, 64]	60.82 years 95% CI [59.7, 62.2]	< 0.001[b]
Gender				
Male	1961 (46.5%)	488 (52.4%)	1473 (44.9%)	< 0.001[c]
Female	2254 (53.5%)	443 (47.6%)	1811 (55.1%)	
Comorbidity (COPD)				
Yes	556 (13.2%)	117 (12.6%)	439 (13.4%)	0.524[c]
No	3659 (86.8%)	814 (87.4%)	2845 (86.6%)	

COPD chronic obstructive pulmonary disease

[a] *p* values refer to differences between former smokers and current smokers

[b] Student's *t* test

[c] χ^2 test

Table 2 Basic characteristics of the study participants according to baseline LCDT screening results

	Negative	Indeterminate	Positive	*p* value[a]
All participants	3127 (74.2%)	914 (21.7%)	174 (4.1%)	
Age (years)				
< 65	2102 (78.1%)	523 (19.4%)	68 (2.5%)	< 0.001[b]
≥ 65	1025 (67.3%)	391 (25.7%)	106 (7.0%)	
Gender				
Male	1429 (72.9%)	455 (23.2%)	77 (3.9%)	0.078[b]
Female	1698 (75.3%)	459 (20.4%)	97 (4.3%)	
Smoking history				
Former smokers	708 (76.1%)	191 (20.5%)	32 (3.4%)	< 0.260[b]
Current smokers	2 419 (73.7%)	723 (22.0%)	142 (4.3%)	
Comorbidity (COPD)				
Yes	369 (66.4%)	153 (27.5%)	34 (6.1%)	< 0.001[b]
No	2 758 (75.4%)	761 (20.8%)	140 (3.8%)	

COPD chronic obstructive pulmonary disease

[a] *p* values refer to differences between the screening result subgroups

[b] χ^2 test

screening outcome in the subsequent round. As for participants with indeterminate results at baseline, positivity occurred in the case of 22 people in the next round (prevalence: 5.6%). Of the 4215 participants initially enrolled in HUNCHEST-II, more than 80% of individuals (n = 3467) did not participate in the second screening examination. Importantly, this low adherence to subsequent-line LDCT scans was less prominent among individuals with indeterminate outcomes in the first round (vs. initially test-negative participants; 42.5% vs. 11.5%, respectively). Accordingly, almost half of those with uncertain outcomes underwent at least another round of LDCT examination. The most common reason behind dropout was the withdrawal of informed consent or changes in the participants' health status. In these later cases, participants were excluded, as per study protocol.

LC incidence and histological distribution among positive screens

A total of 76 LCs were diagnosed throughout the screening rounds, in addition to 55 benign lesions (Fig. 1 and Table 3). Accordingly, the overall PPV of a positive screening test was 58%, meaning that the false-positivity rate was 42%. It should be noted that there is a discussion on what is false positive in LCS—in this paper, we use it as a nodule that is positive in the radiological sense (i.e., size and morphology) but is proven non-malignant in further assessment. Out of all malignant cases, 62 (81.6% of total diagnoses) were already discovered at baseline LDCT screening (Fig. 1). Concerning the initially test-negative group, only 4 LCs were detected in subsequent lines, whereas the number of screen-detected malignancies among participants with indeterminate outcomes was 10 (Fig. 1). Of note, the final diagnosis was unavailable in 74 individuals; accordingly, 63.9% of the positive screening tests led to a diagnostic evaluation. Diagnostic workflow often consisted of further imaging, and when recommended by the multidisciplinary team (MDT), invasive sampling was also performed. Although they occurred rarely, complications of invasive diagnostic procedures included bleeding, airway trauma, and pneumothorax. Histopathological evaluation revealed that most screening-detected LCs were adenocarcinomas (35.5%), followed by squamous cell carcinomas (19.7%) and other malignancies (6.6%) such as large

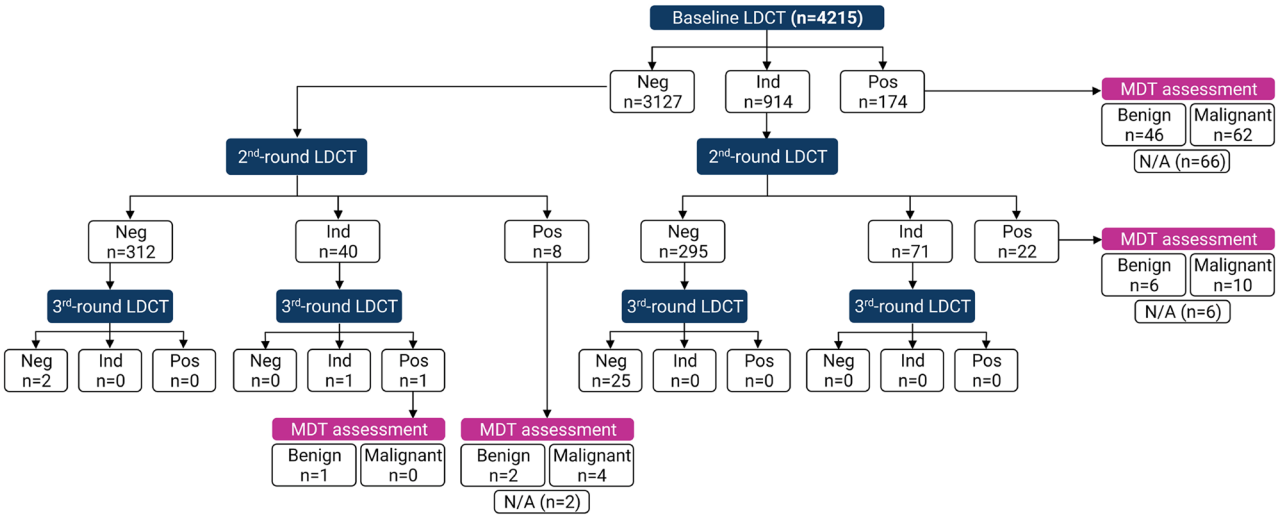

Fig. 1 Participation flowchart of the HUNCHEST-II screening study

Table 3 Histologic features of positive nodules detected in the HUNCHEST-II screening program

	Benign	Malignant	N/A[a]	*p* value[b]	Histological type[c]				
					ADC	SCC	SCLC	Other[d]	N/A[a]
All participants	55 (26.8%)	76 (37.1%)	74 (36.1%)		27 (35.5%)	15 (19.7%)	3 (3.9%)	5 (6.6%)	26 (34.2%)
Age (years)									
< 65	23 (28.4%)	26 (32.1%)	32 (39.5%)	0.485[c]	10 (38.5%)	4 (15.4%)	1 (3.8%)	1 (3.8%)	10 (38.5%)
≥ 65	32 (25.8%)	50 (40.3%)	42 (33.9%)		17 (34.0%)	11 (22.0%)	2 (4.0%)	4 (8.0%)	16 (32.0%)
Gender									
Male	21 (22.3%)	37 (39.4%)	36 (38.3%)	0.410[c]	8 (21.6%)	12 (32.4%)	1 (2.7%)	3 (8.1%)	13 (35.1%)
Female	34 (30.6%)	39 (35.1%)	38 (34.2%)		19 (48.7%)	3 (7.7%)	2 (5.1%)	2 (5.1%)	13 (33.3%)
Smoking history									
Non-smokers or former smokers	10 (27.8%)	11 (30.5%)	15 (41.7%)	0.641[c]	4 (36.4%)	3 (27.3%)	0 (0.0%)	1 (9.1%)	3 (27.3%)
Current smokers	45 (26.6%)	65 (38.5%)	59 (34.9%)		23 (35.4%)	12 (18.5%)	3 (4.6%)	4 (6.2%)	23 (35.4%)
Comorbidity (COPD)									
Yes	12 (29.3%)	10 (24.4%)	19 (46.3%)	0.148[c]	2 (20.0%)	2 (20.0%)	0 (0.0%)	0 (0.0%)	6 (60.0%)
No	43 (26.2%)	66 (40.2%)	55 (33.5%)		25 (37.9%)	13 (19.7%)	3 (4.5%)	5 (7.6%)	20 (30.3%)

ADC adenocarcinoma; *SCC* squamous cell carcinoma; *SCLC* small cell lung cancer; *COPD* chronic obstructive pulmonary disease; *N/A* not available.

[a] Histological diagnosis could not be established due to patient withdrawal

[b] *p* values refer to differences between the *Benign* and *Malignant* subgroups (all patients)

[c] In the case of malignant tumors

[d] Other primary malignancies such as large-cell neuroendocrine carcinoma or carcinoid tumors

[e] χ^2 test

cell neuroendocrine carcinomas or carcinoid tumors (Table 3). Small cell lung cancer (SCLC) was detected at a frequency of 3.9%. Benign lesions most frequently consisted of pulmonary hamartomas and inflammatory nodules. No significant association was found between clinicopathological variables and diagnostic outcomes (benign vs. malignant) (Table 3). The malignant potential of the screen-detected solid and part-solid lesions did not differ significantly.

The impact of LDCT screening on LC stage distribution

In the HUNCHEST-II study, most screen-detected malignancies were stage I LCs (60.7%), whereas only 16.4% of all cases could be classified as stage IV disease

(Supplementary Table 2). To obtain an overview of the benefit of LDCT screening concerning early diagnosis, the outcomes of the first round of screening of HUNCHEST-II were compared with two real-life control groups of 496 and 12,104 LC patients. These matched control groups consisted of LC patients aged between 50 and 75 years from the National Koranyi Institute of Pulmonology's (NKIP) patient archive or from the Hungarian Cancer Registry's nationwide database diagnosed and treated in the same time interval when the HUNCHEST-II screening study was conducted. All individuals in the control groups were considered high-risk individuals as per the HUNCHEST-II study protocol. Notably, none of these patients underwent LDCT screening prior to diagnosis. As shown in Table 4A, LC was substantially more often diagnosed in stage I–IIIA among HUNCHEST-II participants compared to those in the NKIP's database (78.8% vs. 30.5%, respectively; $p < 0.001$). Likewise, stage IV cancer was diagnosed in more than half of the patients in the Hungarian Cancer Registry (59.5%), whereas only 21.2% of the HUNCHEST-II screening-detected LCs were diagnosed in stage IV ($p < 0.001$) (Table 4B). As for therapeutic approaches, all individuals with early-stage disease (including one SCLC patient) underwent lung resection surgery with or without adjuvant chemo- and/or radiotherapy. No postoperative mortality was recorded within 90 days from surgical resection. Patients with late-stage disease received chemotherapy or immunotherapy with or without radiotherapy.

Table 4 (A) LC stage distribution in a matched cohort of the HUNCHEST-II screening program and NKIP database; (B) LC stage distribution in a matched cohort of the HUNCHEST-II screening program and Hungarian Cancer Registry

(A)			
	HUNCHEST II screening program 1st screening round[a]	NKIP database[a]	*p* value[b]
Early stage	48 (78.8%)	151 (30.5%)	< 0.001
Late stage	13 (21.2%)	345 (69.5%)	
All patients	61 (100%)	496 (100%)	
(B)			
	HUNCHEST II screening program 1st screening round[a]	Hungarian Cancer Registry[a]	*p* value[b]
Early stage	48 (78.8%)	4908 (40.6%)	< 0.001
Late stage	13 (21.2%)	7199 (59.5%)	
All patients	61 (100%)	12107 (100%)	

NKIP National Koranyi Institute of Pulmonology, *LC* lung cancer

[a] Only patients with accurate disease staging were included

[b] χ^2 test

Discussion

Early detection strategies such as LDCT screening greatly contribute to the improvement of survival outcomes of LC patients, thus creating a major opportunity to improve public health [8, 10, 12]. Hence, within the framework of the HUNCHEST-II screening program, we estimated the occurrence of pulmonary nodules (including both solid and part-solid lesions) and their LC probability by LDCT in a Hungarian high-risk population.

At baseline, the prevalence of positive screens was 4.1% which is comparable to the NELSON trial (2.3%) [9] and to the pilot HUNCHEST study (3.7%) [17] but considerably lower (27.3%) than in the NLST [8]. This discrepancy is due to the key differences in the nodule evaluation protocols since the NLST used a diameter-based approach, whereas our study adopted a volume-based nodule-management protocol following the Lung-RADS classification system [20]. Importantly, since they substantially reduce the false positivity rates, evaluation protocols based on Lung-RADS are currently the standard for interpreting LDCT images [20, 21]. Accordingly, the overall PPV of positive tests in the HUNCHEST-II was 58%, constituting one of the highest values among all previous screening trials. While this high percentage is undoubtedly promising, the false positivity rate of 42% is still concerning. A recent retrospective study assessing the major factors affecting false positivity found that besides co-existing comorbidities, the radiologists' experience also influences the discovery rates [22]. To overcome this issue, in HUNCHEST-II all specialists were required to evaluate the teaching scans regularly. As for comorbidities, we found that the number of suspicious (i.e., indeterminate or positive) screens was indeed considerably higher in individuals with COPD, an expected finding given that both LC and COPD are associated with smoking. Nevertheless, the number of false positive cases also tends to be higher among COPD patients [23, 24]. The reason for this observation is not fully elucidated, yet the anecdotal clinical experience is that these patients tend to develop benign inflammatory nodules which mimic the presentation of spiculated LC [22]. Lastly, false-positive outcomes are also more frequently associated with baseline scans, as these individuals have no controls to establish the stability of lesions [22]. This phenomenon has been detected previously both in the NELSON and NLST trials [21, 25].

Overall, 76 LC patients were diagnosed throughout the screening rounds in HUNCHEST-II (1.8% of total participants), out of which 62 (1.5%) patients were already identified in the first screening round. This is in line with previous nationwide studies also reporting incidence rates between 0.8 and 2.2% [9, 13, 17, 26–28]. Of note, in the second screening round of initially test-negative individuals, LC was detected in half

of the positive screens. In that sense, the LC probability of a newly developed pulmonary nodule is considerably higher than in the case of baseline lesions, and these require a more aggressive follow-up strategy [10]. VDT, as a plausible indicator of growth rate and tumor aggressiveness contributed to 13.1% of all LC diagnoses. In accordance with the NELSON trial and with other large screening programs, most LCs in our study were adenocarcinomas [9, 11]. One of the fundamental basis on which one undertakes LDCT screening is to identify the malignant lesion as early as possible when it is still readily curable, preferably by surgery. Importantly, 78.8% of all screen-detected LCs were early-stage cancers in HUNCHEST-II, all amenable to surgical resection. This proportion was considerably higher than the incidence rates of early-stage LCs in the NKIP's patient archive and in the Hungarian Cancer Registry, and contributes to significantly lower mortality [9]. With regard to stage distribution, it should also be noted that the percentage of screen-detected early-stage (i.e., stage I–IIIA) LCs did not differ significantly between the pilot HUNCHEST study [17] (conducted before the COVID-19 era) and HUNCHEST-II. During the HUNCHEST-II screening program, a variety of important benign conditions such as severe emphysema, bronchiectasis, and hamartoma were as well detected.

Although overdiagnosis is a nuanced concept, it is frequently raised in LC screening because it might incur unnecessary treatment, follow-up, cost, and patient anxiety [29]. In fact, subsequent analysis of the NLST revealed that a considerable percentage of LCs detected by LDCT seemed to be indolent, and the overall overdiagnosis probability of any LC detected by screening was 18.5% [30]. However, with adequate study planning, the overdiagnosis rate can be minimized. As such, defining a broader spectrum of outcome categories as well as implementing the VDT as a measure of nodule characteristic not only reduces false positivity rate to an acceptable level but also succeeds in omitting indolent LCs while minimizing the risk of overdiagnosis [31]. Accordingly, based on the recommendations of the NELSON trial [9] (and also on the encouraging results of the pilot HUNHCEST screening program [17]), besides positive and negative screening outcomes, a third, indeterminate outcome category was also defined in HUNCHEST-II. Moreover, VDT was also widely used in our study as a plausible indicator of nodule malignancy. As for the role of AI-based computer-assisted diagnosis (CAD) systems in detecting indolent lesions, in a previous validation study, Veye Lung Nodules software only slightly influenced the false positivity rate, which indirectly correlates with overdiagnosis [32]. Given all these, the risk of overdiagnosis was kept minimal in HUNCHEST-II.

Multiple factors hindered our nationwide study. First is the implementation barrier. Although the number of participants adjusted to the country's total population was considerably higher than in other European screening programs such as the Italian ITALUNG [12] or German LUSI [11] trials, only a fraction of eligible citizens has undergone LDCT screening in our study. This slow pace of adoption leaves LDCT-based LC screening much behind approved screening tests for other malignancies [33–35]. Another general issue concerning LDCT screening is that its population-level impact is severely diluted by the strict age- and tobacco-based risk definitions. In this context, minorities with an increased risk of LC, individuals without severe smoking history but with a strong hereditary predisposition, as well as those exposed to second-hand tobacco exposure were excluded from our study [36]. Selection criteria for HUNCHEST-II were milder than in NLST [8] and comparable to the big European trials [9, 11, 12, 14]. The main limitation of our study, however, remains the high attrition rate between the screening rounds. This was especially pronounced in those with initial test-negative results, as only 11.5% of these individuals followed-up with annual screening. These results are alarming since the reduction of LC mortality depends on annual screening, not a single LDCT [37, 38]. Indeed, in some studies, the proportion of screen-detected LCs found after at least one negative screen can reach up to 59% [8]. Understanding the population-based barriers of regular follow-up and promoting the importance of annual screening among high-risk individuals is pivotal to increase adherence in the future. Of note, compliance during the follow-up rounds was undoubtedly hindered by the COVID-19 pandemic. Of note, PPV might also be slightly affected by the COVID-19 pandemic since acute bronchopulmonary infection or post-COVID lesions can simulate malignant processes, thus increasing the number of false-positive outcomes [39]. Lastly, a further limitation constitutes the absence of appropriate participant follow-up and mortality-related data. Therefore, given the lack of close monitoring of test-negative individuals, specificity, sensitivity, and negative predictive value could not be assessed.

HUNCHEST-II demonstrates that LDCT screening for LC facilitates early diagnosis, thus arguing in favor of introducing systematic LC screening in Hungary. Specifically, our screening program contributed to a total of 76 LC diagnoses, with one of the highest PPVs among European trials. The vast majority of these patients were diagnosed with early-stage disease, and the proportion of individuals with late-stage lesions was considerably lower in our study than in the NKIP's patient archive and in the Hungarian Cancer Registry's database. By opening access to curative-intent

treatment, this observed stage shift might subsequently result in a mortality rate reduction in the future. However, some key inquiries remain, such as the optimization of risk-stratified recruitment protocols and the reduction of attrition rate. Altogether, along with other population-based studies, HUNCHEST-II provides further support for LC screening by LDCT and paves the way for even more expansive systematic screening in the region.

Abbreviations

CAD	Computer-aided diagnosis
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CTDI	CT dose index
HUNCHEST	Hungarian LDCT Lung Cancer Screening program
LC	Lung cancer
LDCT	Low-dose computed tomography
MDT	Multidisciplinary team
mGy	Milligray
mSv	Millisievert
NCCN	National Comprehensive Cancer Network
NELSON	Nederlands–Leuvens Longkanker Screenings Onderzoek
NKIP	National Koranyi Institute of Pulmonology (Hungary)
NLST	National Lung Screening Trial (U.S.)
PPV	Positive predictive value
SCLC	Small cell lung cancer
UKLS	UK Lung Cancer Screening Trial
VDT	Volume doubling time

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00330-023-10379-8.

Below is the link to the electronic supplementary material. Supplementary file1 (PDF 249 KB)

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Author contributions
(I) Conception and design AKF, ZM, ZMa, BD, KB; (II) administrative support: PC, KB, JT, AK; (III) provision of study materials or patients: AKF; ZMa, DS,BB, CsP, DT, VM, AS, LU, LT, ZS, CG, AKal, ZsuM, EK, DP, KG, ZH, EC, LK, TJ, Ms, VS, AKov, ZK, AnitaK, ZP, EKI, AD, EV, GG, RTK, IM, ZK; (IV) collection and assembly of data: AKF, ZM, ,PC, JT; (V) data analysis and interpretation: AKF, ZM, ZMa, BD, KB, PC, GM, PR; (VI) manuscript writing: all authors; (VII) Final approval of manuscript: All authors

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Guarantor
The scientific guarantor of this publication is Krisztina Bogos, MD, PhD.

Conflict of interest
Péter Rózsa is the CEO and Senior Health Economist of MediConcept Ltd. Gabriella Merth is an employee of MediConcept Ltd. The remaining authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry
No complex statistical methods were necessary for this paper.

Informed consent
Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval
Institutional review board approval was obtained. The national-level ethics committee (Hungarian Scientific and Research Ethics Committee of the Medical Research Council, approval number: ETT-TUKEB, 002524–005/2014/OTIG) and the local medical board of each participating site approved the study.

Study subjects or cohorts overlap
No study subject overlap

Methodology

- prospective
- diagnostic or prognostic study
- multicenter study

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