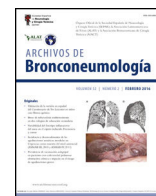




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Scientific Letter

Screened vs. Non-Screened Lung Cancer: Real-World Evidence of a Stage Shift

To the Director,

Lung cancer (LC) remains the leading cause of cancer-related mortality worldwide [1], with 5-year survival rates below 15% due to late-stage diagnosis [2]. In Spain, LC continues to represent a major public health burden, accounting for more than 20,000 new cases and 23,000 deaths annually [3]. Low-dose computed tomography (LDCT) screening has consistently demonstrated substantial reductions in LC-specific mortality among high-risk individuals in large randomized trials [4,5], prompting several European countries—including England, Croatia, and Poland—to implement national programs, alongside the EU-funded 4-IN-THE-LUNG-RUN [6] and the Strengthening the Screening of Lung Cancer in Europe (SOLACE) projects [7].

These initiatives highlight a growing European commitment to structured lung cancer screening (LCS) as a key public health strategy. However, Spain still lacks a national LCS recommendation [8]. Assessing the real-world impact of structured LCS on diagnostic and clinical outcomes is therefore essential to guide future public health policy. To address this evidence gap, the aim of this study was to compare LC cases diagnosed via comprehensive LCS program with those detected through routine clinical practice in Lleida, Catalonia (a region of 12,173 km² and 446,000 inhabitants). This design allows a direct comparison of both diagnostic pathways under real-world conditions.

For this purpose, from May 2023 to October 2025, two LC cohorts were prospectively described and compared at Arnau de Vilanova University Hospital (Lleida, Spain). The study was approved by the local Ethics Committee (CEIC-2783 and CEIC-3153). Written informed consent was obtained in the LCS cohort and was waived for the clinical cohort.

The first included individuals whose LC was detected through a comprehensive LCS program following the International Early Lung Cancer Action Program (I-ELCAP) lung nodule management protocol [9]. Inclusion criteria were age 50–80 years, current smokers or those who had quit the past 15 years with ≥ 20 pack-years. As an alternative eligibility criterion, the smoking cessation time restriction was waived for individuals meeting age and cumulative smoking exposure criteria who had a previously documented diagnosis of chronic obstructive pulmonary disease (COPD) and/or emphysema. COPD had to be confirmed by spirometry according to American Thoracic Society (ATS) criteria, and emphysema had to be previously identified on thoracic CT according to Fleischner Society recommendations. These individuals were primarily recruited from pulmonology outpatient clinics, including COPD follow-up

consultations. Recruitment sources included the Virtual Pulmonary Nodule Assessment Clinic, pulmonology outpatient clinics, and seven primary care centers. Participants underwent annual LDCT and pulmonary function tests. A multidisciplinary LCS committee was established to manage suspicious lesions. Details of the LCS program structure and diagnostic workflow are available elsewhere [10].

The second cohort comprised patients with a histological LC diagnosis through routine clinical practice within the Lleida health area, identified weekly from pathology reports. The cases were typically diagnosed through the regional LC fast-track pathway as part of standard clinical care (hereafter referred to as the clinical cohort).

For both cohorts, clinical data were prospectively recorded and reviewed every six months, including sociodemographic characteristics, smoking history, comorbidities, pulmonary function (American Thoracic Society guidelines), tumor stage (8th edition of the American Joint Committee on Cancer (AJCC) staging system), histologic subtype, treatment, and survival. Descriptive statistics were used to summarize the characteristics of the study population. Qualitative variables were reported as absolute and relative frequencies. The Shapiro–Wilk test was used to assess the normality of quantitative variables, which were presented as mean (standard deviation [SD]) or median (25–75th percentiles) depending on their distribution. Between-group comparisons were performed using *t*-tests or Mann–Whitney *U*-test for continuous variables and Chi-squared tests for categorical variables. Fisher's exact test was applied whenever expected cell counts were ≤ 5 . All analyses were performed using R, version 4.1. Statistical significance was set at a two-sided *p* value of <0.05 .

Between May 2023 and October 2025, 504 high-risk individuals were screened (38.4% women and 61.6% men). Of these, 45 (8.9%) were enrolled under the COPD/emphysema-based eligibility criterion. A total of 18 LC cases were detected through the LCS program and were compared with 290 consecutive LC patients diagnosed through routine clinical practice in the Lleida health area during the same period. Among the 18 screen-detected lung cancers, only one case (5.6%) had been enrolled under the COPD/emphysema-based eligibility criterion; the remaining 17 cases fulfilled standard smoking-based eligibility criteria.

Group comparison of baseline characteristics, including risk model calculators and lung function, are shown in Table 1. Screening-detected LC patients were younger (64.8 [62.3;69.9] vs 69.2 [62.6;75.1], $p=0.09$) and exclusively male (100% vs 74.1%, $p=0.009$). A smoking history was present in 91.0% of the clinical cohort, with comparable tobacco exposure (50.5 [42.5;58.2] vs 48.0 [30.0;62.0] pack-years). Emphysema was identified in all screening-detected cases and in 112 (38.6%) of the clinical cohort ($p<0.001$), while COPD was present in 14 (77.8%) and 63

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Table 1
Comparison of baseline characteristics and diagnostic information between the lung cancer screening and clinical cohorts.

	Screening cohort N = 18	Clinical cohort N = 290	p. value	N
Baseline characteristics				
Age	64.8 [62.3;69.9]	69.2 [62.6;75.1]	0.091	308
Sex, female	0(0.00%)	75(25.9%)	0.009	308
Tobacco history				
Never smoker	0(0.00%)	24(8.33%)	0.566	306
Passive smoker	0(0.00%)	2(0.69%)		
Current smoker	7(38.9%)	89(30.9%)		
Former smoker	11(61.1%)	173(60.1%)		
Pack-years	50.5 [42.5;58.2]	48.0 [30.0;62.0]	0.276	233
Comorbidities				
COPD	14(77.8%)	63(21.7%)	<0.001	308
Emphysema	18(100%)	112(38.6%)	<0.001	308
Atrial fibrillation	4(22.2%)	28(9.66%)	0.065	308
Hypertension	5(27.8%)	154(53.1%)	0.010	308
Heart failure	4(22.2%)	12(4.14%)	0.018	308
Type II diabetes	4(22.2%)	90(31.2%)	0.588	306
Previous oncologic history				
Lung	1(5.56%)	26(8.97%)	1.000	308
Urologic	0(0.00%)	28(9.66%)	1.000	308
Digestive	1(5.56%)	15(5.17%)	1.000	308
Lung function				
FEV ₁ , L	1.80 [1.61;2.09]	2.17 [1.71;2.69]	0.113	208
FEV ₁ , %	65.1 (23.0)	79.6 (21.3)	0.021	207
FVC, L	3.27 [2.96;3.64]	3.15 [2.40;3.76]	0.373	208
FVC, %	83.5 (20.6)	86.2 (18.8)	0.599	207
FEV ₁ /FVC < 70	12(70.6%)	77(40.3%)	0.031	208
DLCO, altered	12(75.0%)	107(60.8%)	0.394	192
TLC, altered	3(20.0%)	61(34.7%)	0.384	191
RV, altered	13(86.7%)	139(79.0%)	0.740	191
Family lung cancer history				
Family lung cancer history	4(22.2%)	43(19.1%)	0.758	243
Risk models				
LLPv3	5.06 [3.72;6.63]	3.11 [0.91;6.06]	0.063	87
PLCOM2014	6.90 [4.28;8.45]	4.23 [1.14;8.94]	0.347	62
Diagnostic data				
Death				
Death	0(0.00%)	130(44.8%)	<0.001	308
Cause of death				
Lung cancer-related		116(90.6%)		128
Respiratory cause		8(6.25%)		
Cardiovascular cause		1(0.78%)		
Unknown		3(2.34%)		
Months to death from any cause		3.32 [1.13;9.60]		130
Months to death from lung cancer		3.59 [1.19;10.2]		116
Stage				
Stage			<0.001	308
I	15(83.3%)	52(17.9%)		
II	0(0.00%)	24(8.28%)		
III	2(11.12%)	51(17.6%)		
IV	1(5.56%)	148(51.0%)		
Death prior to staging				
Death prior to staging	0(0.00%)	12(4.14%)		
Unknown	0(0.00%)	3(1.03%)		
Histology				
Adenocarcinoma	11(61.1%)	181(62.4%)	1.000	308
Squamous cell carcinoma	3(16.7%)	69(23.8%)	0.774	308
Neuroendocrine tumor	0(0.00%)	2(0.69%)	1.000	308
Neuroendocrine carcinoma	2(11.1%)	38(13.1%)	1.000	308
Other	0(0.00%)	7(2.41%)	1.000	305
Treatment				
Surgery				
Surgery	12(66.7%)	79(27.2%)	0.001	308
Curative-intent surgery ^a	12(66.7%)	56(19.4%)		
Radiotherapy				
Radiotherapy	5(27.8%)	65(22.4%)	0.570	308
Curative-intent radiotherapy ^a	3(16.7%)	3(1.04%)		
Chemotherapy				
Chemotherapy	3(16.7%)	146(50.3%)	0.011	308
Immunotherapy				
Immunotherapy	2(11.1%)	92(31.7%)	0.114	308
Targeted therapy				
Targeted therapy	0(0.00%)	22(7.59%)	0.627	308
Palliative				
Palliative	0(0.00%)	34(11.7%)	0.238	308
Death prior to treatment				
Death prior to treatment		23(7.93%)		290
Refused treatment				
Refused treatment		4(1.38%)		290
Unknown		2(0.69%)		290

COPD: chronic obstructive pulmonary disease, FVC: forced vital capacity, FEV₁: forced expiratory volume in first second, TLC: total lung capacity, RV: residual volume, LC: lung cancer, PLCOM2014: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Model 2014, LLPv3: Liverpool Lung Project lung cancer risk stratification model v3. Data are presented as n (%), mean (SD) or median [IQR].

^a Percentage calculated based on the total number of subjects in each cohort.

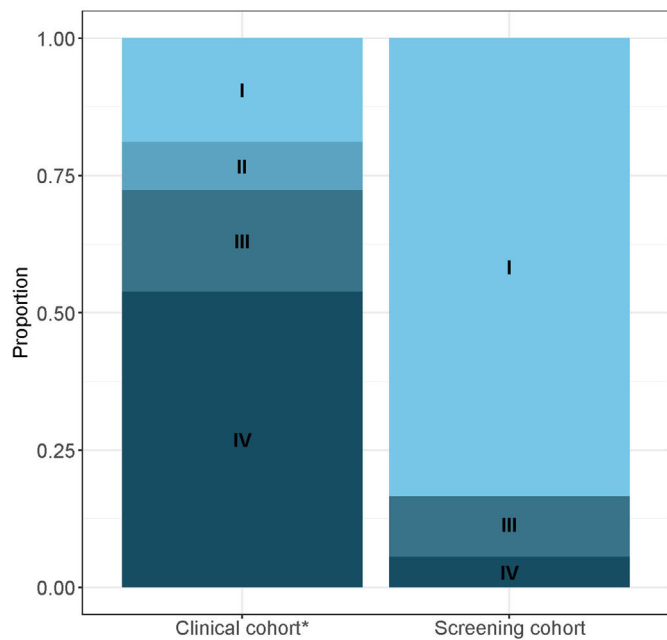


Fig. 1. Lung cancer stage distribution in the screening cohort vs clinical cohort. *Patients with unknown stage or who died before staging were excluded.

(21.7%), respectively ($p < 0.001$) reflecting radiological and spirometric assessment within the LCS program.

Among screening-detected cases, 15 (83.3%) were diagnosed at stage I, whereas 3 (16.7%) presented with advanced disease (stage III and IV). In contrast, in the clinical cohort, 199 (68.6%) patients were diagnosed at advanced stages (III–IV), and 52 (17.9%) and 24 (8.3%) at stages I and II, respectively ($p < 0.001$; Fig. 1). Staging could not be determined in 12 (4.1%) cases due to death before completion of the diagnostic process and was unknown in 3 (1.03%). There were no significant differences in histologic distribution between cohorts, with most cancers being adenocarcinoma ($n = 11$, 61.1% vs. $n = 181$, 62.4%), followed by squamous cell carcinoma ($n = 3$, 16.7% vs. $n = 69$, 23.8%) (Table 1). In two cases from the LCS cohort, histopathological confirmation could not be obtained. One patient’s surgical specimen was damaged and could not be assessed, and the other could not undergo biopsy due to clinical contraindications. Both cases were reviewed by the LCS committee, which unanimously agreed on a LC diagnosis despite the absence of histopathological confirmation. A sensitivity analysis excluding these two cases lacking histopathologic confirmation ($n = 16$) did not materially alter stage distribution, treatment patterns, or between-group comparisons, supporting the robustness of the primary findings (data not shown).

These stage differences were reflected in treatment patterns. Curative-intent therapy was administered to 15 (83.3%) of screening-detected patients—12 (66.7%) underwent surgical resection and 3 (16.7%) received stereotactic body radiotherapy (SBRT)—compared with 59 (20.4%) curative-intent treatment in the clinical cohort, where most received chemotherapy ($n = 146$, 50.3%). At the time of analysis, all screening-detected subjects were alive, whereas 130 (44.8%) individuals in the clinical cohort had died from any cause ($p < 0.001$), of whom 116 (90.6%) died from LC-related causes. The median interval from diagnosis to death among decedents was 3.32 [1.13;9.60] months for all-cause mortality and 3.59 [1.19;10.2] months for LC-specific mortality (Table 1). Retrospective application of LCS eligibility criteria indicated that 58.5% of patients diagnosed through routine care would have qualified for the LCS program. Among these screening-eligible patients, stage distribution remained predominantly advanced: 67.9% were diag-

nosed at stages III–IV, while 18.9% and 8.2% were diagnosed at stages I and II, respectively. Stage was unknown or could not be determined due to death prior to staging in 5.0%.

This prospective comparison is, to our knowledge, the first study in Spain to evaluate LC cases detected through a comprehensive LCS program versus routine clinical practice within the same health-care system. Over two years, a clear stage shift was observed, with 83.3% of screening-detected cases diagnosed at stage I compared with 17.9% in routine care ($p < 0.001$). Curative-intent treatment was offered to 83.3% vs. 20.4% of patients, respectively, and all screening-detected individuals remained alive, contrasting with 44.8% mortality in the clinical cohort. These findings demonstrate the real-world effectiveness of structured lung cancer screening in promoting earlier diagnosis and access to curative treatment.

These results align with international evidence demonstrating that LDCT screening enables earlier detection [4,5,9,11]. The predominance of early-stage diagnoses and adenocarcinoma histology mirrors major screening trials, particularly I-ELCAP [9]. Integrating the LCS program with a comprehensive pulmonary assessment enhanced the identification of high-risk individuals, notably those with COPD or emphysema [12,13]. By contrast, in the absence of systematic LCS, LCs in the clinical cohort were largely diagnosed following symptom onset, 68.6% of cases presenting at advanced stages, comparable to data from the Spanish Thoracic Tumor Registry [14]. Notably, 58.5% of these patients would have met the LCS cohort eligibility criteria [15], suggesting that many could have been detected earlier through structured screening.

The stage shift observed in this study parallels results from other large-scale screening initiatives comparing screened and unscreened populations. In the Hungarian HUNCHEST-II program [16], 78.8% of screen-detected tumors were diagnosed at stage I–IIIA versus 30.5% in unscreened matched controls ($p < 0.001$). Similarly, LDCT screening in Taiwan increased the proportion of stage I diagnoses from 19% to 62.8% and improved five-year survival rates from 22% to 55% [17]. Beyond stage, the detection mode itself carries prognostic value: in the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial [18], screen-detected non-small-cell LC showed longer survival than symptom-detected cases, even after stage adjustment. Likewise, the DELUGE experience confirmed that integrating LDCT screening with structured nodule-management pathways results in a significant stage shift [19].

Strengths of this study include its prospective design within the same healthcare system and period, detailed clinical characterization, and implementation of a structured LCS program with comprehensive respiratory evaluation. Limitations include its single-center, descriptive nature. In the clinical cohort, inclusion was restricted to histologically confirmed diagnoses, potentially excluding clinically suspected LCs. The limited number of screening-detected LCs represents a specific limitation and may have contributed to the observed sex distribution imbalance, with all screen-detected cases occurring in men. Given known sex-related differences in cumulative smoking exposure and respiratory comorbidity, this imbalance could have partially influenced baseline risk profiles and should be considered when interpreting comparisons between the screening and clinical cohorts. Comparisons of time from diagnosis to death between cohorts are inherently subject to lead-time and length bias and should therefore be interpreted with caution. Finally, lung function tests and, mainly, LC risk prediction models, were only available for a subset of the clinical cohort, reflecting data collection in clinical practice, and should be interpreted as exploratory.

In conclusion, LC in the province of Lleida continues to be predominantly diagnosed at advanced stages when detected through routine clinical care, limiting curative treatment options. In contrast, the implementation of a comprehensive LCS program resulted in a substantial shift toward early-stage diagnoses, enabling cura-

tive interventions in most cases. Notably, a high proportion of LCs detected through routine clinical care would have met eligibility criteria for screening. These findings support the expansion of LCS in Spain and its integration into the national healthcare system as an effective public health strategy to improve LC outcomes.

Author contributions

Conceptualization (AS-C, JG), data curation (EG-L, AS-C, NR-S), formal analysis (EG-L, AS-C, JG), investigation (all), methodology (JG, AS-C, SS, CM), project administration (JG, AS-C, NR), supervision (JG, FB), writing – original draft (AS-C, JG), and writing – review & editing (all). All authors provided final approval of the version submitted for publication.

Artificial intelligence involvement

ChatGPT was used to assist with language review during the preparation of this manuscript. The content was subsequently reviewed and edited by the authors, who take full responsibility for its accuracy and integrity.

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Conflicts of interest

The authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.

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