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Impact of Lung Cancer Screening on Stage Migration and Mortality among the National VA Lung Cancer Population

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Précis

Here we aim to show the value of lung cancer screening in a non-randomized, real world setting. VA lung cancer patients who had lung cancer screening prior to diagnosis were diagnosed with earlier stage lung cancer and had decreased mortality compared to those patients who did not undergo screening.

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The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained. All data was retrospectively acquired with IRB approval from the Veterans Health Administration.

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Conflicts of Interest

The authors of this work have no conflicts to report.

CrediT Statement:

Donna M. Edwards: Conceptualization; Investigation; Formal Analysis; Methodology; Visualization; Writing-original draft; Writing-review & editing. **Mina Pirzadeh:** Conceptualization; Investigation; Formal Analysis; Methodology; Visualization; Writing-original draft; Writing-review & editing. **Tony Van**: Conceptualization; Data Curation; Formal Analysis; Investigation; Methodology. **Ralph Jiang**: Conceptualization; Data Curation; Formal Analysis; Investigation; Methodology. **Ashkay Tate**: Data Curation. **Grace Schaefer**: Data Curation. **Jadyn James**: Data Curation. **Caroline Bishop**: Data Curation. **Cydnee Wilson**: Data Curation. **Nicholas Nedzesky**: Data Curation. **Aaron Alseri**: Data Curation. **Anthony Leveque**: Funding

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ABSTRACT

Introduction: Despite randomized trials demonstrating a mortality benefit to low dose computed tomography screening to detect lung cancer, uptake of lung cancer screening (LCS) has been slow, and the benefits of screening remain unclear in clinical practice.

Methods: We aimed to assess the impact of screening among patients in the Veterans Health Administration (VA) healthcare system diagnosed with lung cancer between 2011-2018. We evaluated lung cancer stage at diagnosis, lung cancer specific survival and overall survival between cancer patients who did and did not receive screening before diagnosis. We utilized Cox regression modeling and inverse propensity weighting analyses with lead time bias adjustment to correlate LCS exposure with patient outcomes.

Results: Of 57,919 individuals diagnosed with lung cancer in the VA system between 2011-2018, 2,167 (3.9%) underwent screening before diagnosis. Patients with screening had higher rates of Stage I diagnoses (52% vs 27%, p =<0.0001) compared to those who had no screening. Screened patients had improved 5-year overall survival rates (50.2% vs 27.9%), and 5-year lung cancer specific survival (59.0% vs 29.7%) compared to unscreened patients. Among screening-eligible patients who underwent NCCN guideline-concordant treatment, screening resulted in substantial reductions in all-cause mortality (aHR 0.79, 95% CI: 0.67-0.92, p=0.003) and lung-specific mortality (aHR 0.61, 95% CI 0.50-0.74, p < .001).

Conclusions: Although few Veterans diagnosed with lung cancer had LCS, screening was associated with earlier stage diagnoses and improved survival. This large national study corroborates the value of LCS in clinical practice; efforts to widely adopt this vital intervention are needed.

INTRODUCTION

Lung cancer remains the leading cause of cancer deaths worldwide, and the majority of lung cancer is diagnosed at an advanced stage [1]. Among patients with non-small cell lung cancer (NSCLC), the most common form of lung cancer, 5 year survival for early Stage I disease is approximately 68% compared to a rate of 5.8% for metastatic disease [2]. Thus, prompt detection of early stage disease is paramount to improving outcomes. The U.S. Preventative Services Task Force (USPSTF) currently recommends annual low-dose CT screening for adults between ages 50-80 with at least a 20 pack year smoking history who currently smoke or have quit within the past 15 years. This recommendation is based on randomized trial evidence of a mortality benefit and stage migration effect with screening. The National Lung Screening Trial (NLST)

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demonstrated that use of annual LCS compared to chest X rays in high-risk patients resulted in a relative reduction of 20% in lung cancer mortality [3]. In the NELSON lung screening trial, high risk patients who underwent LCS with CT imaging every 1 to 2.5 years (baseline, 1 year, 3 years, 5.5 years) similarly had decreased lung cancer mortality. Notably, a higher proportion of screening-detected lung cancers were Stage I compared to non-screening-detected cases (58.6% vs 14.2%) [4]. Presumably, the concept of stage migration, or the shift in identifying more earlier stage cancers at time of diagnosis before progression to advanced disease, contributed to the mortality benefit in these trials.

However, the mortality benefits of screening shown on these trials can only be realized with broad implementation of screening in clinical practice, and there remains a need to demonstrate real-world effectiveness of lung cancer screening. There are patient, provider, and system-specific challenges to the implementation of screening [5], resulting in slow adaptation of screening in clinical care. Rates of adherence to screening, which were upwards of 90% on both randomized trials, is lower in the real world setting [6], particularly among black patients [7] and current smokers as well as younger or less educated patients [8]. A recent analysis from the lung cancer screening registry demonstrated that only 1.9% of 7.6 million eligible smokers per NLST criteria underwent screening in 2016 [9]. Variations in patient characteristics of those undergoing screening in practice have the potential to impact the effectiveness of screening. Participants of randomized controlled trials are often more educated or healthier than the general population, and such disparities in real-world patients from trial patients may raise concern over the applicability of trial results into the general population who are often more elderly, frail or with more medical comorbidities [6]. It is also possible that implementation of screening in practice has been impacted by provider concern for overdiagnosis and treatment of cancers that would have otherwise remained indolent [4, 10, 11]. Additional concerns involve adequate infrastructure available to support comprehensive screening programs, as noted in a survey of pulmonologists in the VA system [12].

The Veterans Health Administration (VHA) is the largest integrated provider of cancer care, caring for approximately 6.7 million Veterans a year system-wide [13]. There is a heightened prevalence of smoking among Veterans with military service [14-16], resulting in an estimated 76% higher age-specific incidence of lung cancer than the general population [17]. The Lung Cancer Screening Demonstration Project (LCSD) through the Veteran's Health Administration estimated that nearly 900,000 patients of a population of 6.7 million VA patients would be eligible for lung cancer screening [13]. However, there is limited VHA data beyond single site reports [18, 19] to

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assess effectiveness of lung cancer screening to diagnosis cancer at an earlier stage. In this study we performed a retrospective analysis of 57,919 Veterans in the national VA lung cancer registry diagnosed with lung cancer between 2011-2018 to assess whether lung cancer screening influences outcomes of Veterans with lung cancer.

METHODS

Study design

The national VA lung cancer registry was retrospectively reviewed to identify patients diagnosed with lung cancer between the years of 2011 to 2018. This time period was chosen to encompass the years during which time we would expect to see screening become more utilized in clinical practice, after publication of the NLST trial. Demographic and clinical variables were extracted from the lung cancer registry at the time of diagnosis. Cancer stage was determined based on the AJCC system currently in use at the time of diagnosis, and patients with Stage 0 lung cancer were excluded from the analysis due to small numbers. Staging from the lung cancer registry was confirmed by manual chart review in a subset of 50 patients to ensure consistency between the registry and EMR. The diagnosis of lung cancer included all primary lung cancers, such as adenocarcinoma, squamous cell carcinoma, and small cell lung cancer. Information on smoking history was obtained via a natural language processing (NLP) algorithm to identify smoking pack-years and quit date status that was then manually verified. The main exposure variable of interest was LCS, and patients were considered to have had screening if they had at least one low dose CT (LDCT) prior to the date of their lung cancer diagnosis identified on the basis of ICD9/10 codes. The outcome of overall survival was obtained from date of diagnosis until death or last known follow up within the EMR. Lung cancer specific mortality was then extracted from the cancer registry and merged with National Death Index (NDI) data using ICD coded lung specific cause-of-death (C33 or C34). This study was reviewed and approved by the Institutional Review Board at the Ann Arbor VA.

Statistical Analyses

Statistical analyses were performed utilizing R (R version 4.1.2) and Graph Pad Prism. Comparisons in baseline characteristics between “LCS” and “no LCS” cohorts were made using chi-squared and Wilcoxon tests. To account for the lead-time bias resulting from earlier disease detection by screening, an estimated correction time was subtracted from each patient’s observed survival time. The expected additional survival time observed solely due to lead time in the screened patients was estimated according to the method in Duffy et al [20]. Survival functions

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were estimated with the Kaplan-Meier method and compared among “LCS” and “no LCS” cohorts using the log-rank test. We also defined a separate subset of patients from the overall cohort to be “screening-eligible.” “Screening-eligible” patients were defined as those between the ages of 50-80, who were smokers with pack year history ≥ 20 years or former smokers who quit within 15 years, and who underwent guideline-concordant treatment within 12 months of diagnosis. Multivariate cox modeling was performed with this “screening-eligible” subset of patients. To estimate the effect of screening on eligible patients, inverse probability treatment weighting (IPTW) analysis was performed in a Cox regression. To do this, we developed a propensity scoring model to predict prior LCS exposure using: age, gender, race, ethnicity, smoking status, pack years, and comorbidity score. For each patient, we estimated their propensity score for LCS and computed inverse probability treatment weights (IPTW) for LCS exposure status. Standardized mean differences before and after IPTW indicated that any covariate imbalances between the screened and unscreened groups had been eliminated by the weighting. The mean sojourn time for lung cancer required for this method was estimated from a meta-analysis by Chien et al [21].

Patient and Public Involvement

The research questions addressed in this study directly reflect our goal to improve lung cancer patient outcomes. It is known that despite randomized trial evidence and USPSTF recommendations, lung cancer screening has not been widely adopted. We hope that this study will inspire patients, physicians, hospital administrators and policymakers alike to improve implementation of this intervention and save more lives with early cancer detection. Patients were not directly involved in the study design, and all data was retrospectively acquired with IRB approval from the Veterans Health Administration (IRB 1638998).

RESULTS

A total of 57,919 individuals were diagnosed with lung cancer in the VA system between the years 2011-2018. Of these patients, 2,167 (3.9%) underwent screening, with at least one LDCT prior to their lung cancer diagnosis. Baseline characteristics of the patients and characteristics of the diagnosed lung cancers are shown in **Table 1**, **Table 2** and **Supplemental Table 1**.

There were no significant differences in age, gender or race among patients who had prior screening (“LCS” cohort) and those without prior screening (“no LCS” cohort) (**Table 1**). There were more non-Hispanic patients (p=0.002) and less non-smokers (p<0.001) among the patients who were screened compared to unscreened. Additionally, there were more adenocarcinomas

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and less squamous cell carcinoma diagnoses in the screened group compared to those diagnosed without screening (p<0.001). An uptake in screening was particularly noted after 2014, with increasing proportion of patients diagnosed with lung cancer after screening over time, for example 2.9% of the total screened cohort in 2014 to 44% by 2018 (**Supplemental Figure 1**).

We explored whether prior LCS exposure would correlate to a stage shift and earlier diagnosis of lung cancer. Screened patients had double the rate of Stage I diagnoses compared unscreened patients, 52% vs 27%, p=<0.0001, as well as a lower proportion of Stage IV diagnoses, 11% vs 32%, p =<0.0001 (**Table 2**, **Figure 1, Supplemental Table 2**). The incidence of each stage of lung cancer (I-IV) by year among screened and unscreened patients is shown in **Supplemental Figure 2**, and the trend towards higher incidence of Stage I lung cancer and lower incidence of Stage IV cancers among screened patients is consistent, particularly in the years 2014-2018 in which uptake in screening in this cohort is most notable (**Supplemental Figure 1**).

Corresponding with the heightened incidence of Stage 1 lung cancers in the screened cohort, we also observed improved overall survival among patients who received screening prior to their cancer diagnosis (**Figure 2A**). The 1 year, 2 year, and 5 year overall survival rates were 81.2%, 69.9% and 44.9%, and 56.6%, 41.1% and 22.3% for the screened cohort and the unscreened cohort, respectively (p<0.0001). Lung cancer specific survival is similarly heightened among those undergoing screening (**Figure 2B**). The 1 year, 2 year and 5 year lung cancer specific survival rates were 82.5% vs 58.7%, 74.3% vs 44.4%, and 59.0% vs 29.7%, for screened versus unscreened cohorts, respectively (p<0.0001).

We further explored the impact of screening within a defined subset of patients deemed “screening eligible.” This subset of our entire cohort was defined as those patients between the ages of 50-80, who were smokers with pack year history ≥ 20 years or former smokers who quit within 15 years, and who underwent guideline-concordant treatment within 12 months of diagnosis. Of our total cohort of 57,919 patients, 10,075 (17.4%) were determined to be screening-eligible. Multivariate Cox modeling of this subset showed that screening was associated with a sizeable decrease in all cause mortality (aHR 0.46, 95% CI 0.4-0.54, p<0.0001) and lung cancer specific death (aHR 0.37, 95% CI 0.31-0.45, p<0.0001) (**Figure 3A-B**). Cox modeling using an IPTW approach showed similar results (**Supplemental Figure 3**). Finally, as a further sensitivity analysis, we also incorporated the IPTW with a lead-time bias adjustment as described in our methodology and observed continued association of screening with improvement in all-cause mortality (aHR 0.79, 95% CI: 0.67-0.92, p=0.003) and the lung-specific mortality (aHR 0.61, 95% CI 0.50-0.74, p < .001).

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Propensity score modeling of the "screening eligible" subset further revealed that patients who had a smoking history (aOR 1.26, 95% CI 1.09, 1.47, p=0.002) or were Black (aOR 1.2, 95% CI 1.04-1.43, p=0.016) were more likely to have been screened, while Hispanic patients (aOR 0.56, 95% CI 0.3-0.93, p=0.0391) and patients with more comorbidities (aOR 0.87, 95% CI 0.83-0.91, p≤0.0001) were less likely to have screening (**Supplemental Table 3**).

DISCUSSION

Despite robust randomized clinical trial data demonstrating a mortality benefit to lung cancer screening [3, 4], we observed that only a small minority of Veterans with lung cancer (3.9%) obtained a LDCT prior to their lung cancer diagnosis, similar to other reported rates [20]. However, the use of screening in this small subset of Veterans was associated with a compelling stage migration effect as well as an improvement in overall survival and lung cancer specific survival, presumably due to cancer diagnosis and intervention at an earlier stage of disease. Multivariate cox modeling of the screening-eligible population subset showed that use of screening was strongly associated with decreased overall mortality as well as lung specific mortality. To our knowledge, this is the largest retrospective cohort of lung cancer patients quantifying the real-world impact of lung cancer screening among Veterans, a population enriched in smokers at high risk of developing lung cancers [16].

Our results are in line with other studies that have similarly highlighted the value of implementation of screening into routine clinical care. A US National Cancer Database and SEER database analysis showed a population-level increase in diagnosis of Stage I NSCLC in the years 2014-2018 coinciding with recommendations for LCS [21]. Additionally Robertson et. al [22] utilized a transportability analysis in a comparative effectiveness study to estimate the effects of LCS on a national population of NLST-eligible U.S. adults and estimated a persistent lung cancer mortality benefit to screening in this target population. Our data similarly captures the benefit of LCS in a high-risk patient popuation that differs in baseline covariates from clinical trial participants. Vachani et al also noted in a multicenter retrospective cohort of over 3,000 patients that among those who underwent screening prior to a diagnosis of lung cancer, there was a stage migration to detecting more early-stage lung cancers [23]. Our analysis builds on and corroborates these previous studies at a patient-level, and our work is unique in that we have been able to assess the differences in outcomes not only between lung cancer patients who did and did not undergo screening, but also quantify the impact of screening among screening-eligible patients who

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subsequently received lung cancer-directed therapy, the most relevant population for clinical practice.

This study has its limitations, namely the retrospective and correlative nature of the design. We utilized robust statistical methods such as IPTW with lead time bias adjustment to minimize otherwise unmeasured confounding. Additionally, about 10% of patients in the screened cohort were classified as non-smokers. We suspect that this may reflect misclassification in the electronic medical record, and thus these data are limited in scope for the understanding of the impact of smoking status on outcomes. We were also unable to assess whether LCS contributed to more subsquent procedures in screened patients compared to unscreened patients due to the complexity in capturing the range of relevant procedures such as bronchoscopy or CT-guided biopsy, and inability to assess for potential confounding by patients for whom diagnosis triggered empiric treatment rather than additional procedures. Capturing such data would be an important goal for future study to fully appreciate the impact of LCS in clinical practice.

These findings provide corroboration of the results of the randomized lung cancer screening trials in clinical practice. We hope that the striking association between lung cancer screening, earlier stage diagnosis of lung cancer and improved mortality spurs a more robust uptake of this life-saving intervention into clinical practice.

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TABLES AND FIGURE LEGENDS

Table 1. Patient characteristics among patients in the VA cancer registry from 2011-2018.

Patient Characteristics	All patients (n=57,919)	Cohort 1: LCS (n=2,167)	Cohort 2: no LCS (n=55,752)	P value (Cohort 1 vs Cohort 2)
Age				0.603
Median (range)	69 (64, 75)	69 (66, 73)	68 (64, 75)	
Gender (%)				0.175
Female	1,550 (2.7%)	68 (3%)	1,482 (2.7%)	
Male	56,369 (97.3%)	2,099 (97%)	54,270 (97.3%)	
Race (%)				0.381
Asian	144 (0.2%)	7 (0.3%)	137 (0.3%)	
Black	9,506 (16.4%)	342 (15.7%)	9,164 (16.4%)	
Native American	302 (0.5%)	9 (0.4%)	293 (0.5%)	
Pacific Islander	338 (0.6%)	11 (0.5%)	327 (0.6%)	
White	45,333 (78.3%)	1,709 (78.9%)	43,624 (78.2%)	
Other	378 (0.7%)	21 (1%)	357 (0.6%)	
Unknown	1,918 (3.3%)	68 (3.1%)	1850 (3.3%)	
Ethnicity				0.002
Non-hispanic	54,942 (94.9%)	2,087 (96.3%)	52,855 (94.8%)	
Hispanic	1,343 (2.3%)	29 (1.3%)	1,314 (2.4%)	
Unknown	1,634 (2.8%)	51 (2.4%)	1,583 (2.8%)	
Smoking status				< 0.001
Non-smoker	7,054 (12.2%)	222 (10.2%)	6,832 (12.3%)	
Former smoker	12,262 (21.2%)	504 (23.3%)	11,758 (21.1%)	
Current Smoker	24,497 (42.3%)	1,124 (51.9%)	23,373 (41.9%)	
Unknown	14,106 (24.4%)	317 (14.6%)	13,789 (24.7%)	
Alive (%)				< 0.001
	13,464 (23.3%)	1,235 (57.0%)	12,229 (21.9%)	
Follow up time, years				< 0.001
	2.22 (0.41, 3.34)	2.48 (1.49, 3.37)	1.34 (0.39, 3.34)	

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Table 2. Cancer characteristics among patients in the VA cancer registry from 2011-2018.

Cancer Characteristics	All patients (n=57,919)	Cohort 1: LCS (n=2,167)	Cohort 2: no LCS (n=55,752)	P value (Cohort 1 vs Cohort 2)
Stage				< 0.001
I	16,570 (28.6%)	1,136 (52.4%)	15,434 (27.7%)	
II	5,279 (9.1%)	185 (8.5%)	5,094 (9.1%)	
III	10,594 (18.3%)	292 (13.5%)	10,302 (18.5%)	
IV	18,281 (31.6%)	250 (11.5%)	18,031 (32.3%)	
Unknown	7,195 (12.4%)	304 (14%)	6,891 (12.4%)	
Histology				0.002
Adenocarcinoma	24,662 (42.6%)	993 (45.8%)	23,669 (42.5%)	
Squamous cell carcinoma	19,844 (34.3%)	674 (31.1%)	19,170 (34.4%)	
Other	13,123 (22.7%)	495 (22.8%)	12,628 (22.7%)	
Unknown	290 (0.5%)	5 (0.2%)	285 (0.5%)	

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Figure 1. Stage migration of lung cancer diagnoses between 2011-2018 among screened and unscreened patients. **** = p<0.0001 via chi square.

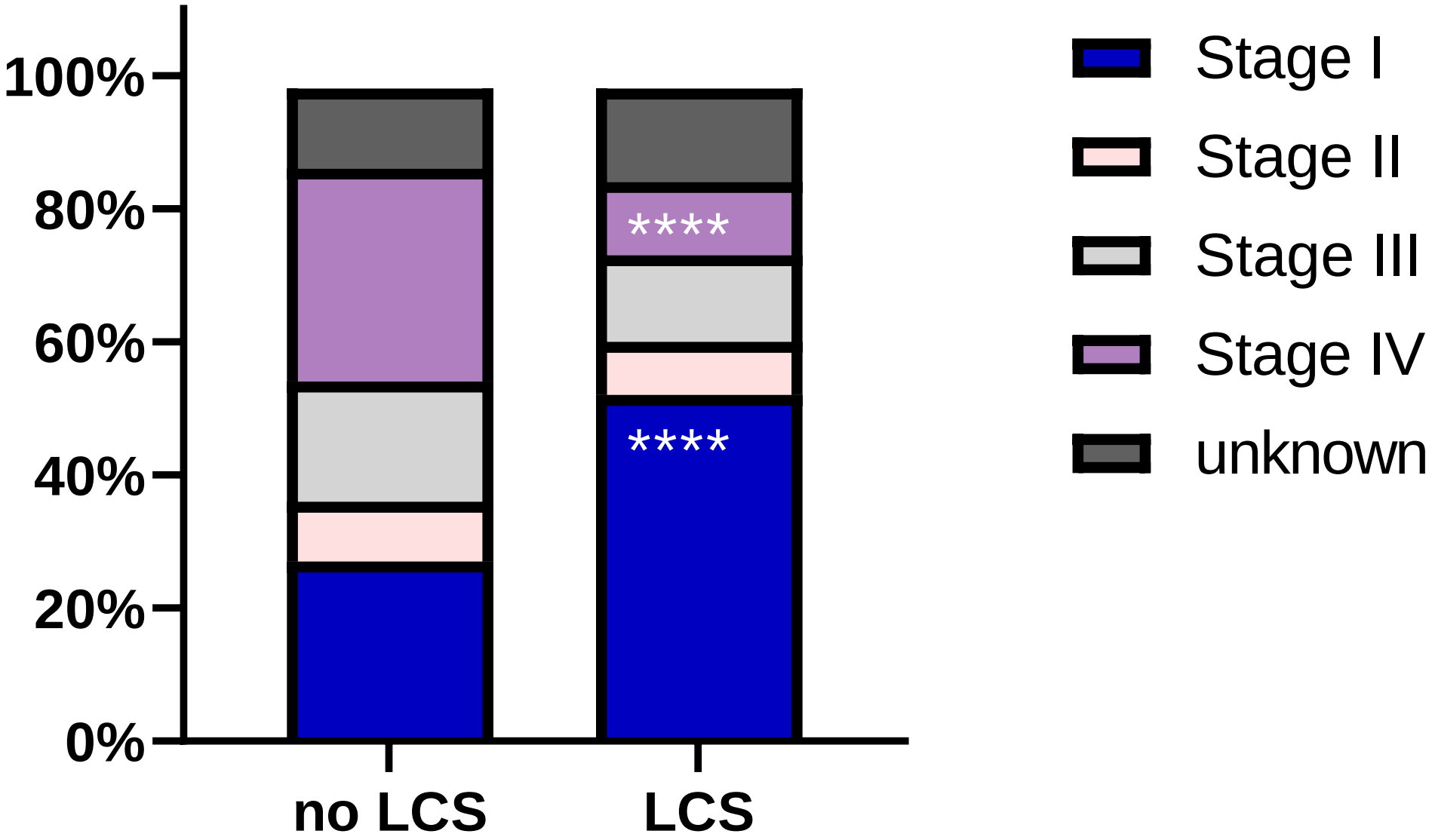
Figure 2. A) Overall survival of lung cancer patients who received LCS (+ LCS) compared to those that did not receive screening (- LCS) prior to diagnosis. Overall survival calculated from date of diagnosis to date of death or censoring at last known follow up. B) Lung cancer specific survival between lung cancer patients who did (+LCS) and did not (-LCS) undergo screening prior to diagnosis. Data censored after 5 years post diagnosis.

Figure 3. Cox modeling of baseline factors associated with all cause mortality (A) and lung specific mortality (B) among screen-eligible patients. aHR = adjusted Hazard Ratio; 95% CI = 95% confidence interval.

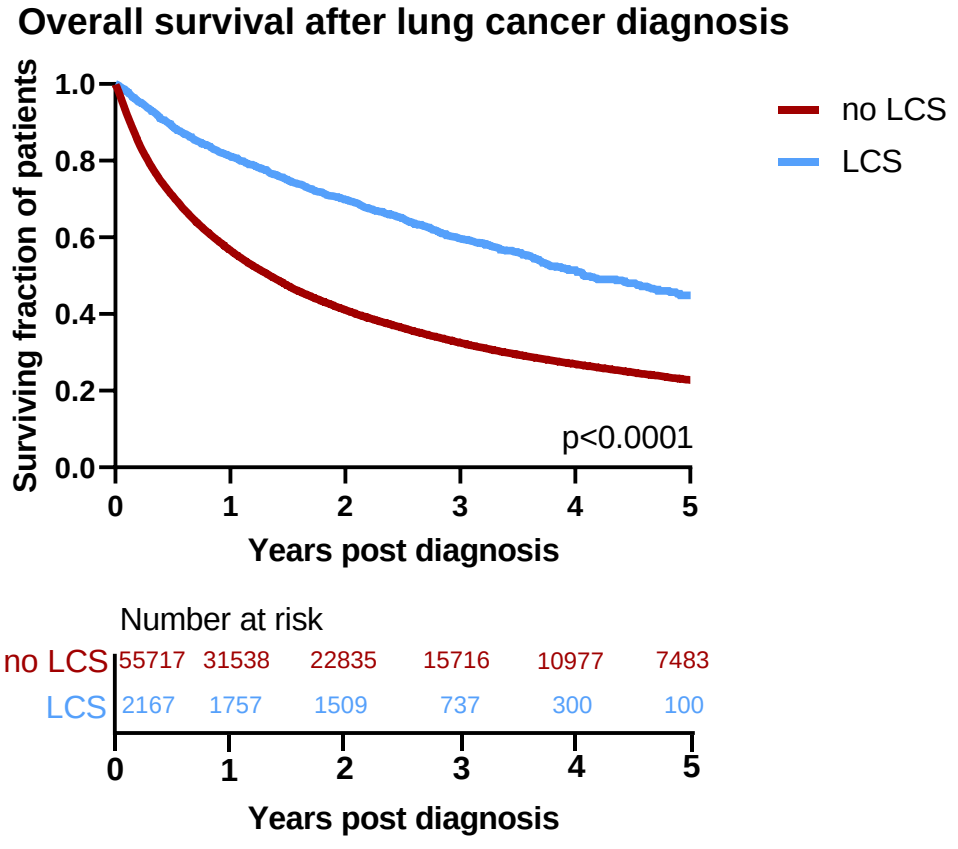
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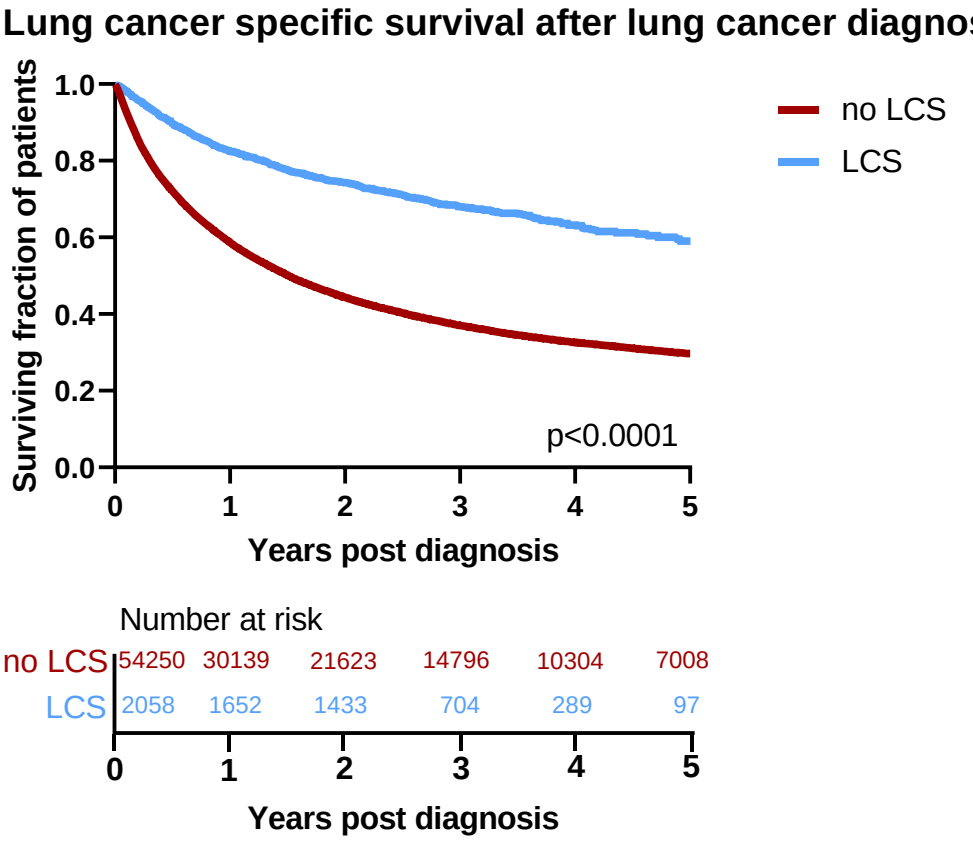
Lung cancer stage at diagnosis

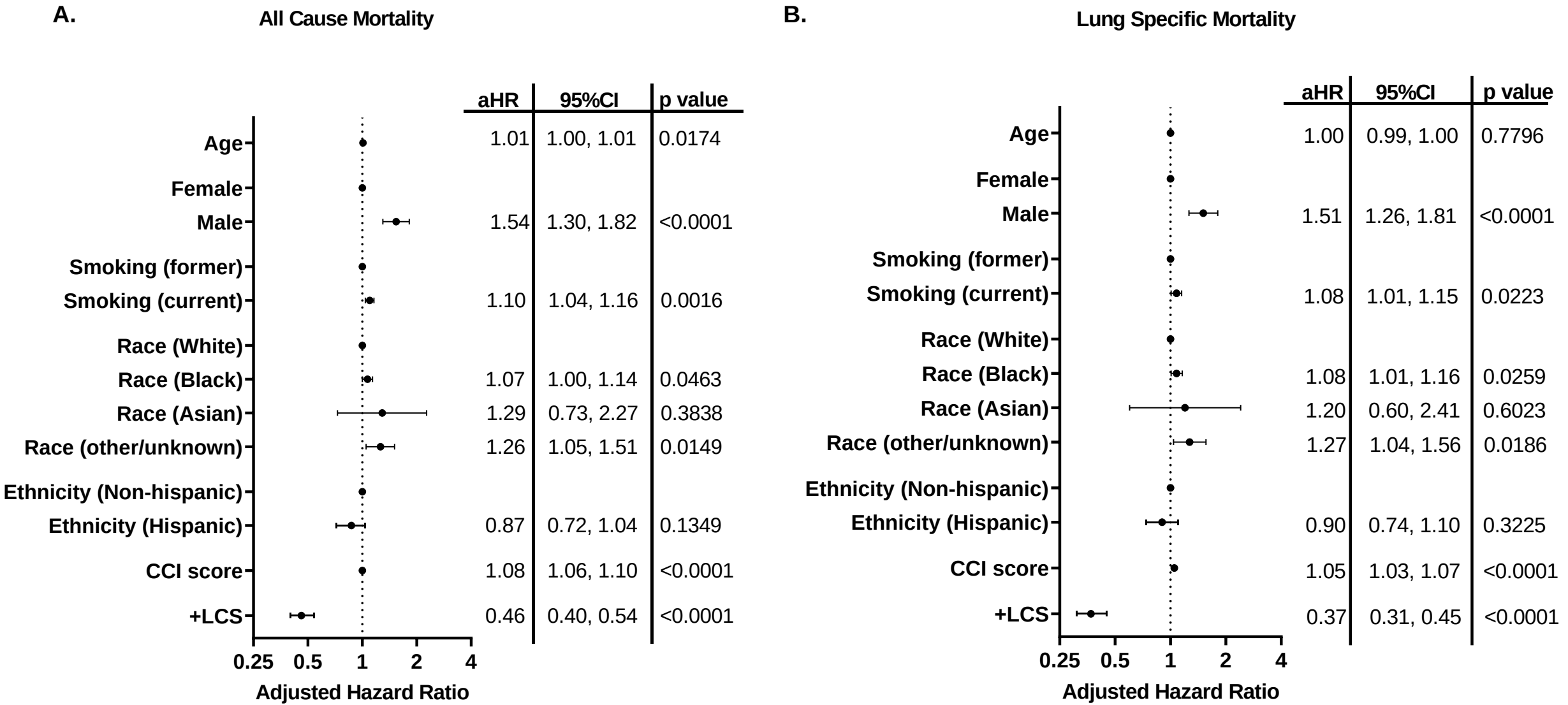


A.


Overall survival after lung cancer diagnosis
Surviving fraction of patients
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Years post diagnosis
no LCS
LCS
p<0.0001
Number at risk
no LCS 55717 31538 22835 15716 10977 7483
LCS 2167 1757 1509 737 300 100
Years post diagnosis

B.


Lung cancer specific survival after lung cancer diagnosis
Surviving fraction of patients
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Years post diagnosis
no LCS
LCS
p<0.0001
Number at risk
no LCS 54250 30139 21623 14796 10304 7008
LCS 2058 1652 1433 704 289 97
Years post diagnosis


A.
All Cause Mortality
aHR
95%CI
p value
Age
1.01
1.00, 1.01
0.0174
Female
Male
1.54
1.30, 1.82
<0.0001
Smoking (former)
Smoking (current)
1.10
1.04, 1.16
0.0016
Race (White)
Race (Black)
1.07
1.00, 1.14
0.0463
Race (Asian)
1.29
0.73, 2.27
0.3838
Race (other/unknown)
1.26
1.05, 1.51
0.0149
Ethnicity (Non-hispanic)
Ethnicity (Hispanic)
0.87
0.72, 1.04
0.1349
CCI score
1.08
1.06, 1.10
<0.0001
+LCS
0.46
0.40, 0.54
<0.0001
0.25
0.5
1
2
4
Adjusted Hazard Ratio
B.
Lung Specific Mortality
aHR
95%CI
p value
Age
1.00
0.99, 1.00
0.7796
Female
Male
1.51
1.26, 1.81
<0.0001
Smoking (former)
Smoking (current)
1.08
1.01, 1.15
0.0223
Race (White)
Race (Black)
1.08
1.01, 1.16
0.0259
Race (Asian)
1.20
0.60, 2.41
0.6023
Race (other/unknown)
1.27
1.04, 1.56
0.0186
Ethnicity (Non-hispanic)
Ethnicity (Hispanic)
0.90
0.74, 1.10
0.3225
CCI score
1.05
1.03, 1.07
<0.0001
+LCS
0.37
0.31, 0.45
<0.0001
0.25
0.5
1
2
4
Adjusted Hazard Ratio