Impact of diabetes on stage I lung cancer treatment patterns and prognosis in older adults: A population-based cohort study

Amanda Leiter [a,*], Christian Stephens [b], Grace Mhango [b], Chung Yin Kong [b], Keith Sigel [b], Jenny J. Lin [b], Emily J. Gallagher [a], Derek LeRoith [a], Juan P. Wisnivesky [b,c]

[a] *Division of Endocrinology, Diabetes, and Bone Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1055, New York, NY, 10029, USA*
[b] *Division of General Internal Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1087, New York, NY, 10029, USA*
[c] *Division of Pulmonary and Critical Care Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1232, New York, NY, 10029, USA*

ARTICLE INFO

ABSTRACT

Background: Diabetes is a common comorbidity in patients with early-stage non-small cell lung cancer (NSCLC), a growing population due to increased LC screening. However, it is unknown if diabetes is associated with less aggressive NSCLC treatment and worse NSCLC outcomes. This study aimed to investigate treatment patterns and outcomes of older patients with Stage I NSCLC and diabetes.

Methods: Using national cancer registry data linked to Medicare, we identified patients ≥65 years old with Stage I NSCLC. Patients were categorized as having no diabetes, diabetes without severe complications (DM-c), or diabetes with ≥1 severe complication (DM + c). We used multinomial logistic regression to assess the association of diabetes and NSCLC treatment. The association of diabetes category with NSCLC and non-NSCLC survival was analyzed with Fine-Grey competing-risks regression.

Results: In 25,358 patients (75% no diabetes, 12% DM-c and 13% had DM + c), adjusted analyses showed that DM-c and DM + c were associated with increased odds of receiving limited resection rather than lobectomy (odds ratio [OR]: 1.22, 95% confidence interval [CI]: 1.07–1.37 and OR 1.42, 95% CI 1.26–1.59, respectively). Competing risk regression showed diabetes was associated with increased risk of non-NSCLC death (DM-c hazard ratio [HR] 1.16, 95% CI: 1.08–1.25, DM + c HR 1.49, 95% CI: 1.40–1.59), but not NSCLC-specific death.

Conclusion: This study uncovers critical information on how diabetes is associated with less aggressive early-stage NSCLC care in older patients. This study also confirms that diabetes increases death from non-lung cancer causes and managing comorbidities is crucial to improving outcomes in older early-stage NSCLC survivors.

* Corresponding author.
  E-mail address: Amanda.Leiter@mssm.edu (A. Leiter).

1. Introduction

Lung cancer is the primary cause of cancer-related deaths globally and in the United States. Non-small cell lung cancer (NSCLC) accounts for over 85% of cases mainly affecting older adults (with a median age of 70 at diagnosis) [1–3]. Thanks to increased lung cancer screening, NSCLC is now being detected at earlier stages [4]. Meanwhile, diabetes has emerged as a significant public health concern, particularly among adults aged 65 and above, with a prevalence of 25% [5]. Consequently, diabetes is relatively common among older patients with NSCLC and contributes to substantial morbidity and mortality [6].

Similar to the general population, diabetes is considered a risk factor for worse overall survival in NSCLC patients, especially those with locoregional disease who undergo surgery [6–9]. However, studies examining the impact of diabetes on NSCLC prognosis and survival have produced conflicting results and have not specifically focused on older adults [6,9]. Treatment guidelines for early-stage NSCLC are primarily based on randomized controlled trials that often exclude or underrepresent older patients with comorbidities like diabetes [10,11]. Therefore, treatment decisions for these patients rely on the care team's evaluation of each patient, which can be particularly challenging for those with diabetes complications due to their increased susceptibility to adverse events from surgery, chemotherapy, and radiation [12–16].

The standard treatment for Stage I NSCLC is lobectomy, which involves removing the entire lobe of the lung [17]. However, limited resection, where only the tumor and surrounding margins are removed, is often chosen for patients with a high risk of complications. For inoperable Stage I lung cancer patients, stereotactic body radiation therapy (SBRT) is the preferred treatment, and it may also be an alternative to limited resection for operable patients with a high surgical risk [18]. Patients with diabetes and end-organ damage such as myocardial infarction, nephropathy, or severe peripheral vascular disease are often deemed high risk for surgery or medically inoperable (as per definitions used by NSCLC randomized control trials cited in NSCLC treatment guidelines), leading to less aggressive treatment [19–21]. Despite the significance of this issue, there is limited data on treatment patterns and the impact of management on NSCLC outcomes in patients with diabetes. Therefore, this study aimed to investigate treatment patterns and mortality rates among older adults with Stage 1 NSCLC and diabetes in a large, nationally representative US cohort.

2. Material and methods

To conduct this study, we utilized a cohort derived from the Surveillance, Epidemiology, and End Results (SEER) registry, which was linked to Medicare claims for patients diagnosed with NSCLC 2004 through 2015 with follow-up data through 2017 [22]. Our inclusion criteria consisted of patients aged 65 or above (CDC definition of older adult and age to qualify for Medicare) with histologically confirmed Stage I NSCLC diagnosed between 2004 and 2015 and pre-existing type 2 diabetes [23]. We included patients after 2004, as this was when SBRT started being adopted into clinical practice for treatment of Stage I NSCLC [24]. The staging of NSCLC was determined based on the American Joint Committee on Cancer (AJCC) 8th edition criteria [25], utilizing information reported by SEER, such as tumor size, extension, lymph node involvement, and metastasis. Exclusions were made for patients enrolled in health maintenance organizations, those without Medicare Part B coverage resulting in incomplete claims data, and cases with insufficient follow-up or demographic information.

Our primary focus was on diabetes as the main exposure variable, considering the presence or absence of severe end-organ complications. We investigated type 2 diabetes, as this makes up >90% of cases worldwide [5]. We employed validated claims-based algorithms to identify patients with preexisting type 2 diabetes that preceded NSCLC diagnosis [26]. The severity of diabetes complications was determined using the Diabetes Complications Severity Index (DCSI), which is a validated claims-based tool [27]. The DCSI assigns a severity score for seven categories of diabetes complications, including cardiovascular, renal, retinopathy, peripheral vascular disease, cerebrovascular accident, neuropathy, and metabolic complications (diabetic ketoacidosis). Minor complications were assigned a score of 1, while severe complications received a score of 2 [26,27]. Patients with diabetes and a score of 0 or 1 across the seven complication categories were categorized as having no complications or minor complications (DM-c). Patients with diabetes and a DCSI score of >2 in any of the seven categories were classified as having severe end-organ complications (DM + c).

Our study focused on two primary outcomes. Firstly, we examined the primary treatment approaches for NSCLC in patients with no diabetes, DM-c and DM + c. Information regarding NSCLC treatment was obtained from SEER-Medicare claims data. Surgical intervention within 6 months of diagnosis was determined using surgical codes, while radiation therapy and SBRT within 6 months of diagnosis were identified using Healthcare Common Procedure Coding System codes and Medicare procedure codes [28,29]. Receipt of chemotherapy within 4 months of NSCLC diagnosis was recorded based on claims-based data [30]. Secondly, we assessed overall survival (OS) and lung cancer-specific survival (LCSS) in patients without diabetes, DM-c and DM + c. Survival time was calculated from the date of diagnosis to the date of death, with LCSS determined from death certificate information provided by SEER. Patients alive as of 2017 were censored at that timepoint.

Additional variables of interest were extracted from the SEER-Medicare databases, including sociodemographic information, comorbidities, NSCLC AJCC 8th edition stage, NSCLC tumor characteristics (size and location), and year of NSCLC diagnosis. To assess comorbidity burden, a modified Charlson comorbidity index score was calculated, excluding diabetes and cancer [31,32].

2.1. Statistical analysis

Baseline patient characteristics and treatment type were compared between patients without diabetes, DM-c and DM + c with the chi-square test . We conducted multinomial logistic regression analyses to assess differences in patterns for the primary treatment of Stage I NSCLC in patients without diabetes, DM-c and DM + c while controlling for confounders. We evaluated differences in initial

treatment (no treatment, lobectomy, limited resection [wedge resection and segmentectomy], SBRT, and other [chemotherapy and/or standard radiotherapy]) in patients with Stage I NSCLC. In the model, covariates were age, sex, marital status, race/ethnicity, income quartile, modified Charlson comorbidity score, chronic obstructive pulmonary disease, lung cancer tumor site, tumor location, and year of lung cancer diagnosis.

As competing risks of death are a major consideration in patients with diabetes and Stage I NSCLC, we conducted a multivariable Fine-Grey competing risks regression to estimate the impact of diabetes category on the hazards of death from lung cancer and death from other causes. We generated unadjusted cumulative incidence function (CIF) curves for probability of death from lung cancer and probability of death from other causes. Covariates in the Fine-Grey model included risk factors known to impact survival, including age, sex, marital status, race/ethnicity, income quartile, modified Charlson comorbidity score category, chronic obstructive pulmonary

Table 1
Baseline patient characteristics according to diabetes category.

Characteristic	Total N (%) N = 25,358	No Diabetes N = 18,919	Diabetes Without or with Minor Complications N = 3074	Diabetes with Major Complications N = 3365	P-Value
Sociodemographic Characteristics					
Age category, N (%)					<0.0001
<70 years	5291 (21)	3959 (21)	709 (23)	623 (19)	
70–74.9 years	7163 (28)	5276 (28)	943 (31)	944 (28)	
75–79.9 years	6499 (25)	4801 (25)	769 (25)	929 (28)	
80–84.9 years	4325 (17)	3274 (17)	456 (15)	595 (18)	
>85 years	2080 (8)	1609 (9)	197 (6)	274 (8)	
Female, N (%)	14,072 (55)	10,817 (57)	1671 (54)	1584 (47)	<0.0001
Race, N (%)					<0.0001
White	21,872 (86)	16,678 (88)	2431 (79)	2763 (82)	
Black	1551 (6)	954 (5)	290 (9)	307 (9)	
Hispanic	777 (3)	487 (3)	149 (5)	141 (4)	
Other	1158 (4.5)	800 (4)	204 (7)	154 (5)	
Income Quartile, N (%)					<0.0001
1st	7254 (29)	5284 (28)	956 (31)	1014 (30)	
2nd	6458 (25)	4776 (25)	784 (26)	898 (27)	
3rd	5680 (22)	4239 (22)	678 (22)	763 (23)	
4th	5966 (24)	4620 (24)	656 (21)	690 (21)	
Married, N (%)	13,217 (52)	9873 (52)	1600,952)	1744 (52)	0.93
Modified Comorbidity Score, N (%)					<0.0001
<1	10,101 (40)	7027 (36)	2145 (68)	1253 (36)	
1–2	11,490 (45)	9878 (50)	787 (25)	1185 (34)	
>2	3767 (15)	2644 (14)	215 (7)	1043 (30)	
Chronic obstructive pulmonary disease, N (%)	14,003 (55)	10,131 (54)	1684 (55)	2188 (65)	<0.0001
Tumor Characteristics					
Year of diagnosis					<0.0001
2004–2006	6227 (25)	4862 (26)	741 (24)	624 (19)	
2007–2009	6381 (25)	4765 (25)	876 (29)	740 (22)	
2010–2012	6288 (25)	4577 (24)	833 (27)	898 (27)	
2013–2015	6462 (25)	4735 (25)	624 (20)	1103 (33)	
Tumor Site, N (%)					0.28
Upper lobe	15,052 (59)	11,256 (60)	1826 (59)	1970 (59)	
Middle lobe	1395 (6)	1039 (5)	177 (6)	179 (5)	
Lower lobe	8168 (32)	6094 (32)	979 (32)	1095 (33)	
Other	743 (3)	530 (3)	92 (3)	121 (4)	
Tumor size, N (%)					<0.0001
0–2 cm	10,873 (43)	8220 (43)	1317 (43)	1336 (40)	
2–3 cm	8389 (33)	6238 (33)	957 (31)	1194 (36)	
3–4 cm	5636 (22)	4151 (22)	722 (23)	763 (23)	
Unknown	460 (2)	310 (2)	78 (3)	72 (2)	
Histology, N (%)					<0.0001
Adenocarcinoma	14,137 (56)	10,874 (57)	1583 (52)	1680 (50)	
Squamous Cell	7586 (30)	5446 (29)	956 (31)	1184 (35)	
Other/Unknown	3635 (14)	2599 (14)	535 (17)	501 (15)	

disease, and year of lung cancer diagnosis. For lung cancer-specific survival models, analyses also adjusted for lung cancer treatment category, lung cancer tumor site, tumor size, and histology. We conducted competing risk analyses stratified by lung cancer year of diagnosis, treatment type, and comorbidity index score category.

Based on the sample size of patients with Stage I NSCLC in SEER-Medicare, we hand >80% power to identify >2% differences in probability of treatment type and we had >80% power to predict a 20% relative difference in conditional probabilities for causes of death that are >15% all observed deaths. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC) using two-tailed p values. *P*-values <0.05 were considered statistically significant.

2.2. Ethics statement

The Icahn School of Medicine at Mount Sinai Institutional Review Board approved this study (IRB 16–00576) and waved inform consent in compliance with the Code for Federal Regulations Title 45 Part 46.116. The study was conducted in compliance with the Declaration of Helsinki (2013).

3. Results

From the SEER-Medicare database, we identified 26,177 patients aged 65 and above with Stage I NSCLC. After exclusions, 25,358 patients were included in the analysis (237 with missing follow-up data and 582 with missing income data). The average follow-up time was 4 years. Among these patients, 18,919 (75%) had no diabetes, 3074 (12%) had DM-c, and 3365 (13%) had DM + c (Table 1).

Patients with DM-c were more likely to be in younger age groups (23% below 70 years old) compared to those without diabetes (21% below 70 years old) and patients with DM + c (19% below 70 years old, p < 0.0001). A higher percentage of patients with DM + c were male (p < 0.0001), identified as Black race (p < 0.0001), and had lower income (belonging to the bottom two income quartiles) (p < 0.01) compared to patients without diabetes or DM-c. Patients with DM + c had a later NSCLC diagnosis year (33% after 2013) compared to patients with DM-c (20% after 2013) and no diabetes (25% after 2013, p < 0.0001). There was no statistically significant difference in tumor site across diabetes categories (p = 0.28) and patients without diabetes (43%) and DM-c (43%) were more likely to have smaller tumors (0–2 cm) than patients with DM + c (40%, p < 0.0001).

In unadjusted analysis (Table 2), patients with DM + c, DM-c, and no diabetes differed in terms of treatment management (p < 0.0001). Overall, 41% of patients with Stage I NSCLC with DM + c underwent lobectomy compared to 50% of patients without diabetes and 52% of patients with DM-c. Patients with DM + c were also more likely to receive no treatment or SBRT. In adjusted analyses (Table 3), patients with DM-c were significantly more likely to undergo limited resection than lobectomy (odds ratio [OR]: 1.22, 95% confidence interval [CI]: 1.07–1.37) compared to those without diabetes. However, patients with DM-c were not significantly more likely to undergo SBRT (OR: 0.89, 95% CI: 0.76–1.05) or receive other/no treatment (OR: 0.91, 95% CI: 0.82–1.01) compared to patients without diabetes. Patients with DM + c were significantly more likely to undergo limited resection (OR: 1.42, 95% CI: 1.26–1.59) and SBRT (OR: 1.62, 95% CI: 1.43–1.83) than lobectomy compared to patients without diabetes.

In this cohort, there were 8,107 non-lung cancer-related deaths and 8,049 lung cancer deaths. Unadjusted CIF curves are shown by diabetes category in patients with NSCLC for lung cancer death (Fig. 1A) and non-lung cancer death (Fig. 1B). Competing risk regression analysis (Table 4) showed that DM-c (hazard ratio [HR]: 1.16, 95% CI: 1.08–1.25) and DM + c (HR: 1.49, 95% CI: 1.40–1.59) were associated with an increased risk of non-lung cancer death compared to those without diabetes. However, DM-c (HR: 1.01, 95% CI 0.94–1.08) and DM + c (HR: 1.04, 95% CI: 0.97–1.12) were not significantly associated with an increased risk of lung cancer-specific death. In analyses stratified by year of lung cancer diagnosis, DM-c and DM + c were not associated with an increased risk of lung cancer death. In all diagnosis year categories, DM + c was associated with an increase in non-lung cancer death. DM-c was associated with non-lung cancer death in patients diagnosed 2004–2009, but not 2010–2015. For all lung cancer treatment categories, DM-c and DM + c were not associated with increased risk of lung cancer death. However, DM-c and DM + c were both associated with higher non-lung cancer death for patients who received lobectomy, but only DM + c (and not DM-c) was associated with non-lung cancer mortality for other treatment categories. In patients with a modified Charlson comorbidity index score of zero, DM + c was associated with higher hazard of lung cancer death (HR: 1.18, 95% CI: 1.04–1.35), but DM-c was not (HR: 1.09, 95% CI: 0.98–1.22). In this group, DM-c and DM + c were both associated with increased hazard of non-lung cancer death. In patients with higher comorbidity index scores (1 and ≥ 2), DM-c and DM + c did not significantly increase lung-cancer specific mortality. In these groups, only DM + c, but not DM-c had an association with increased non-lung cancer death.

Table 2
Association of diabetes with stage I non-small cell lung cancer primary treatment: Unadjusted.

Lung Cancer Treatment Category	Total N = 25,358	No Diabetes N = 18,919	Diabetes Without or with Minor Complications N = 3074	Diabetes with Major Complications N = 3365	*P*-Value
Lobectomy	12,507 (49)	9545 (50)	1599 (52)	1363 (41)	<0.0001
Limited Resection	3392 (13)	2429 (13)	450 (15)	513 (15)	
SBRT	2589 (10)	1886 (10)	220 (7)	483 (14)	
Other or None	6870 (27)	5059 (27)	805 (26)	1006 (30)	

Table 3

Association of diabetes with stage I non-small cell lung cancer primary treatment: Adjusted.[a]

Lung Cancer Treatment Category	Diabetes Without or with Minor Complications		Diabetes with Major Complications	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Lobectomy	Reference		Reference	
Limited Resection	1.22	1.07–1.37	1.42	1.26–1.59
SBRT	0.89	0.76–1.05	1.62	1.43–1.83
Other or None	0.91	0.82–1.01	1.12	1.02–1.24

[a] Adjusted with age, sex, race/ethnicity, income, marital status, modified Charlson comorbidity index, chronic obstructive pulmonary disease, tumor size, tumor site, tumor histology, year of lung cancer diagnosis.
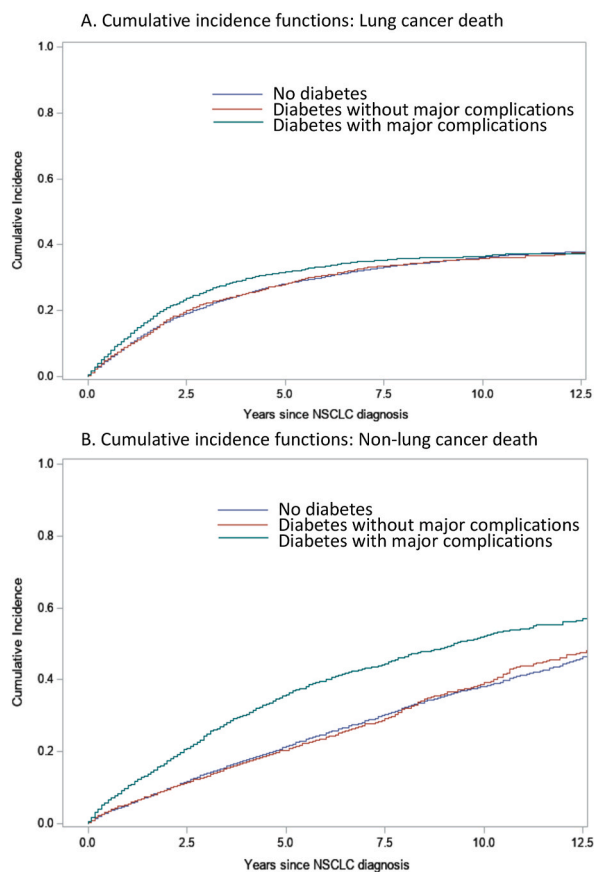
Fig. 1. Cause-specific cumulative incidence function curves by diabetes category in patient with non-small cell lung cancer (NSCLC) for A. Lung cancer death; B. Non-lung cancer death.

4. Discussion

In this study, we aimed to investigate the impact of DM-c and DM + c on the treatment patterns and prognosis of Stage I NSCLC in older patients. Our findings revealed that both DM + c and DM-c were associated with less aggressive treatment for NSCLC. Specifically, patients with DM-c were more likely to undergo limited resection instead of lobectomy, while patients with DM + c were more likely to receive both limited resection and SBRT. Furthermore, we observed that patients with DM-c and DM + c had worse overall survival, but no significant association was found between diabetes status and lung cancer-specific prognosis. Interestingly, patients without diabetes, DM-c, and DM + c who received less aggressive treatments for Stage I lung cancer (treatments other than lobectomy) experienced increased lung cancer-specific deaths. This suggests that diabetes does not directly affect lung cancer progression but serves as a competing cause of death, potentially diminishing the long-term benefits of NSCLC treatment in older patients.

Our study benefited from a large, national cancer dataset comprising a diverse group of older patients from various geographic regions, thereby enhancing the generalizability of our results to the US population. Additionally, the inclusion of long-term follow-up data for most patients allowed for comprehensive assessment of survival outcomes.

Table 4

Lung cancer-specific and non-lung cancer mortality of patients according to diabetes category and lung cancer treatment category: Competing risks regression.

Diabetes Category	Lung Cancer-Specific Survival Hazard Ratio (95% Confidence Interval)[a]	Non-Lung Cancer Survival Hazard Ratio (95% Confidence Interval)[b]
FULL COHORT (N = 25,358)		
No diabetes	REF	REF
Diabetes without severe complications	1.01 (0.94–1.08)	1.16 (1.08–1.25)
Diabetes with severe complications	1.04 (0.97–1.12)	1.49 (1.40–1.59)
STRATIFICATION VARIABLE		
YEAR OF DIAGNOSIS		
2004–2006 (N = 6227)		
No diabetes	REF	REF
Diabetes without severe complications	1.02 (0.90–1.17)	1.21 (1.06–1.37)
Diabetes with severe complications	1.03 (0.90–1.18)	1.42 (1.25–1.62)
2007–2009 (N = 6381)		
No diabetes	REF	REF
Diabetes without severe complications	1.00 (0.88–1.14)	1.18 (1.04–1.34)
Diabetes with severe complications	0.94 (0.82–1.08)	1.57 (1.39–1.77)
2010–2012 (N = 6288)		
No diabetes	REF	REF
Diabetes without severe complications	0.93 (0.80–1.08)	1.15 (0.99–1.33)
Diabetes with severe complications	1.10 (0.96–1.26)	1.48 (1.31–1.68)
2013–2015 (N = 6462)		
No diabetes	REF	REF
Diabetes without severe complications	1.14 (0.93–1.41)	1.02 (0.83–1.25)
Diabetes with severe complications	1.02 (0.87–1.20)	1.42 (1.24–1.62)
LUNG CANCER TREATMENT TYPE		
Lobectomy (N = 12507)		
No diabetes	REF	REF
Diabetes without severe complications	1.02 (0.90–1.15)	1.29 (1.17–1.43)
Diabetes with severe complications	1.06 (0.94–1.21)	1.72 (1.56–1.90)
Limited resection (N = 3392)		
No diabetes	REF	REF
Diabetes without severe complications	1.14 (0.94–1.38)	1.08 (0.90–1.31)
Diabetes with severe complications	1.01 (0.83–1.22)	1.55 (1.32–1.83)
Stereotactic Body Radiation Therapy (N = 2589)		
No diabetes	REF	REF
Diabetes without severe complications	1.01 (0.78–1.30)	1.19 (0.93–1.52)
Diabetes with severe complications	0.91 (0.75–1.12)	1.29 (1.10–1.52)
Other or None (N = 6870)		
No diabetes	REF	REF
Diabetes without severe complications	0.97 (0.87–1.09)	1.08 (0.94–1.23)
Diabetes with severe complications	1.07 (0.97–1.18)	1.28 (1.13–1.43)
MODIFIED CHARLSON COMORBIDITY INDEX SCORE		
0 (N = 10101)		
No diabetes	REF	REF
Diabetes without severe complications	1.09 (0.98–1.22)	1.20 (1.08–1.34)
Diabetes with severe complications	1.18 (1.04–1.35)	1.47 (1.30–1.67)
1 (N = 11490)		
No diabetes	REF	REF
Diabetes without severe complications	0.93 (0.81–1.08)	1.1 (0.97–1.25)
Diabetes with severe complications	0.98 (0.87–1.10)	1.5 (1.40–1.71)
≥ 2 (N = 3767)		
No diabetes	REF	REF
Diabetes without severe complications	0.89 (0.71–1.13)	1.00 (0.80–1.24)
Diabetes with severe complications	0.94 (0.83–1.07)	1.34 (1.20–1.49)

[a] Adjusted with age, sex, race/ethnicity, home health aide, income, marital status, modified Charlson comorbidity index, chronic obstructive pulmonary disease, tumor size, tumor site, tumor histology, lung cancer treatment category, year of lung cancer diagnosis.

[b] Adjusted with age, sex, race/ethnicity, home health aide, income, marital status, modified Charlson comorbidity index, chronic obstructive pulmonary disease, year of lung cancer diagnosis, if stratified does not include stratification variable.

It is important to acknowledge the limitations of this study. Firstly, diabetes status was determined based on diagnosis codes, lacking detailed information on factors such as glucose data or diabetes duration. However, we utilized a validated retrospective claims-based algorithm to evaluate the severity of diabetes complications. Furthermore, the analysis did not incorporate the use of anti-hyperglycemic medications due to data availability constraints, as information was only accessible for a subset of patients with Medicare Part D claims. We also lacked data pertaining to other potential confounders, such as smoking and body mass index. With SEER-Medicare data, we also were not able to ascertain recurrence, limiting our ability to assess recurrence-free survival as an outcome. Additionally, our dataset included patients diagnosed through 2015. While this allows for ample follow-up data for a large

amount of our cohort, this may limit generalizability to a more updated early-stage NSCLC population. However, primary therapies for Stage I NSCLC have been largely unchanged over the past decade, so the findings from this study are still relevant.

Our analysis aligns with existing literature demonstrating that patients with diabetes tend to receive less aggressive cancer treatment [33]. This observation holds true specifically for NSCLC, where a higher comorbidity burden is associated with less aggressive treatment, particularly for Stage I disease [34]. A previous study by Gould et al. found that diabetes with macrovascular complications (e.g. cardiovascular, cerebrovascular) rather than microvascular complications (e.g. nephropathy, retinopathy) was linked to a decreased likelihood of receiving preferred treatment, particularly for Stage 0-II lung cancer [34]. However, their study did not focus on older patients, explore the impact of varying degrees of diabetes complications on treatment patterns, or consider the potential role of SBRT as an alternative treatment option to surgery. In contrast, our study specifically demonstrates that older patients with diabetes, regardless of the severity of complications and after accounting for comorbidity index and tumor characteristics, were more likely to undergo limited resection rather than lobectomy. Moreover, older patients with diabetes and severe complications were more likely to receive SBRT. This study confirms the hypothesis that older patients with diabetes and Stage I NSCLC generally receive less aggressive treatment. However, it is noteworthy that many older patients with diabetes and end-organ complications in our study still underwent surgery, indicating that the criteria for medical inoperability due to diabetes are not frequently applied in real world settings. This may be attributed to the lack of explicit guidelines regarding medical inoperability, as they are often found in references within clinical guidelines [21]. Unfortunately, randomized controlled trials of NSCLC treatment tend to exclude patients with severe comorbidities, leaving the benefits of novel treatments in older patients with diabetes and severe complications, as well as other comorbidities, uncertain. Consequently, providing guidance for patients with comorbidities poses a challenge, and our study emphasized the need to evaluate optimal treatment approaches in these individuals.

Our results highlight that diabetes represents a significant competing risk of death for lung cancer, contributing to worse overall survival in older patients with early-stage lung cancer. This finding is expected considering the mortality associated with diabetes and its complications. Previous literature on this subject aligns with our results, although there is limited data focusing on older early-stage patients with NSCLC who receive treatment other than surgery. A recent meta-analysis demonstrated that diabetes worsens overall survival in surgically treated NSCLC, consistent with our findings [9]. Another meta-analysis examining studies encompassing stage 0-IV NSCLC patients indicated that preexisting diabetes adversely affects NSCLC overall survival [6]. A more recent analysis from claims data in Germany also demonstrated that DM-c was associated with a moderate ($<7\%$) drop in overall survival (all stages), which is consistent with our study showing increased non-lung cancer death in patients who underwent lobectomy [35]. Another recent study examining early-stage squamous cell NSCLC who received surgery showed that DM + c had worse overall survival than DM-c, but these groups were not compared to those without diabetes [36]. Diabetes likely exacerbates overall survival largely by increasing the risk of death from cardiovascular disease and other vascular complications [7]. Additionally, evidence suggests that diabetes and cardiovascular conditions receive less aggressive treatment during cancer treatment [37,38].

Furthermore, our study indicates that diabetes may not increase the progression of lung cancer. Our findings align with small observational studies involving approximately 100–900 participants, which indicate that DM does not increase the risk of lung cancer-specific death [9]. In our study, we expanded upon these results by investigating this association in a large population-based cohort of older adults. In competing risks analyses stratified by modified Charlson comorbidity score, DM + c was significantly associated with worse lung cancer-specific mortality in patients with the lowest overall comorbidity burden (with DM-c having a non-significant association). In this population, DM + c perhaps reflects microvascular complications not reflected in the Charlson comorbidity score, which may reflect a different diabetes subtype or worse hyperglycemia that increases lung cancer aggressiveness. The inflammatory pathways that drive microvascular outcomes, like neuropathy and retinopathy, that would not be reflected in the Charlson score, are also known to drive cancer growth [39,40]. The outcomes from stratified analyses should be interpreted with caution, as these are exploratory analyses and some results are expected to differ. The relationship between diabetes and lung cancer-specific outcomes differs from many other malignancies such as breast and colon cancer, where diabetes worsens cancer-specific outcomes. The relationship between diabetes and NSCLC is complex. While NSCLC is not generally regarded as a diabetes-associated cancer, studies have shown that measures of insulin resistance, including insulin levels and increased waist circumference, are associated with a higher risk of developing lung cancer [41–44].

5. Conclusions

To summarize, our study demonstrated that older patients with Stage I NSCLC and diabetes, regardless of the presence of end-organ complications, were less likely to undergo aggressive treatment for NSCLC. Moreover, they experienced similar lung cancer-specific mortality rates and worse overall survival compared to patients without diabetes. Awareness of how diabetes impacts clinical outcomes in survivors of early-stage lung cancer, a group that typically has more favorable lung cancer prognosis, could help to further risk-stratify these patients. Further research focusing on the influence of diabetes control and treatment on lung cancer outcomes will provide valuable insights into the impact of diabetes on the clinical outcomes of early-stage lung cancer patients.

Author contribution statement

Amanda Leiter: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Christian Stephens: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Grace Mhango: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or

data; Wrote the paper.

Chung Yin Kong; Keith Sigel: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Jenny J. Lin; Emily J. Gallagher; Derek LeRoith: Analyzed and interpreted the data.

Juan P. Wisnivesky: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: EJG has served on an advisory board for Novartis pharmaceuticals and as a consultant for Seattle Genetics and SynDevRx. DLR has served on the advisory boards for Mannkind and Astra Zeneca. JPW reports consulting honoraria from Atea, Sanofi, and Banook, and PPD and research grants from Sanofi, Regeneron and Arnold Consultants. AL, CS, GM, KS, JJL, and CYK have no disclosures to report.

References

[1] R. Govindan, N. Page, D. Morgensztern, W. Read, R. Tierney, A. Vlahiotis, et al., Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database, J. Clin. Oncol. 24 (2006) 4539–4544, https://doi.org/10.1200/jco.2005.04.4859.

[2] R.L. Siegel, K.D. Miller, H.E. Fuchs, A. Jemal, Cancer statistics, CA Cancer J Clin. 2022 72 (2022) 7–33, https://doi.org/10.3322/caac.21708.

[3] Howlader N NA, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2017. Bethesda, MD: National Cancer Institute.

[4] A.K. Ganti, A.B. Klein, I. Cotarla, B. Seal, E. Chou, Update of incidence, prevalence, survival, and initial treatment in patients with non-small cell lung cancer in the US, JAMA Oncol. 7 (2021) 1824–1832, https://doi.org/10.1001/jamaoncol.2021.4932.

[5] Prevention CfDCa, National Diabetes Statistics Report, 2020, Centers for Disease Control and Prevention, US Department of Health and Human Services, Atlanta, GA, 2020.

[6] G. Bi, G. Yao, Y. Bian, L. Xue, Y. Zhang, T. Lu, et al., The effect of diabetes mellitus on prognosis of patients with non-small-cell lung cancer: a systematic review and meta-analysis, Ann. Thorac. Cardiovasc. Surg. 26 (2020) 1–12, https://doi.org/10.5761/atcs.ra.19-00170.

[7] J. Pearson-Stuttard, J. Bennett, Y.J. Cheng, E.P. Vamos, A.J. Cross, M. Ezzati, et al., Trends in predominant causes of death in individuals with and without diabetes in England from 2001 to 2018: an epidemiological analysis of linked primary care records, Lancet Diabetes Endocrinol. 9 (2021) 165–173, https://doi.org/10.1016/s2213-8587(20)30431-9.

[8] J.M. Baena-Díez, J. Peñafiel, I. Subirana, R. Ramos, R. Elosua, A. Marín-Ibañez, et al., Risk of cause-specific death in individuals with diabetes: a competing risks analysis, Diabetes Care 39 (2016) 1987–1995, https://doi.org/10.2337/dc16-0614.

[9] H.Y. Deng, X. Zheng, P. Zha, L. Peng, K.L. Huang, X.M. Qiu, Diabetes mellitus and survival of non-small cell lung cancer patients after surgery: a comprehensive systematic review and meta-analysis, Thorac Cancer 10 (2019) 571–578, https://doi.org/10.1111/1759-7714.12985.

[10] J.M. Unger, D.L. Hershman, M.E. Fleury, R. Vaidya, Association of patient comorbid conditions with cancer clinical trial participation, JAMA Oncol. 5 (2019) 326–333, https://doi.org/10.1001/jamaoncol.2018.5953.

[11] L.F. Hutchins, J.M. Unger, J.J. Crowley, C.A. Coltman Jr., K.S. Albain, Underrepresentation of patients 65 years of age or older in cancer-treatment trials, N. Engl. J. Med. 341 (1999) 2061–2067, https://doi.org/10.1056/nejm199912303412706.

[12] M.K. Ferguson, P. Saha-Chaudhuri, J.D. Mitchell, G. Varela, A. Brunelli, Prediction of major cardiovascular events after lung resection using a modified scoring system, Ann. Thorac. Surg. 97 (2014) 1135–1140, https://doi.org/10.1016/j.athoracsur.2013.12.032.

[13] Y. Tokunaga, Y. Kita, T. Okamoto, Analysis of risk factors for bronchopleural fistula after surgical treatment of lung cancer, Ann. Thorac. Cardiovasc. Surg. 26 (2020) 311–319, https://doi.org/10.5761/atcs.oa.20-00010.

[14] C. Johnson, V.S. Pankratz, A.I. Velazquez, J.A. Aakre, C.L. Loprinzi, N.P. Staff, et al., Candidate pathway-based genetic association study of platinum and platinum-taxane related toxicity in a cohort of primary lung cancer patients, J. Neurol. Sci. 349 (2015) 124–128, https://doi.org/10.1016/j.jns.2014.12.041.

[15] D.L. Hershman, C. Till, J.D. Wright, D. Awad, S.D. Ramsey, W.E. Barlow, et al., Comorbidities and risk of chemotherapy-induced peripheral neuropathy among participants 65 Years or older in southwest oncology group clinical trials, J. Clin. Oncol. 34 (2016) 3014–3022, https://doi.org/10.1200/jco.2015.66.2346.

[16] R.T. Dess, Y. Sun, M.M. Matuszak, G. Sun, P.D. Soni, L. Bazzi, et al., Cardiac events after radiation therapy: combined analysis of prospective multicenter trials for locally advanced non-small-cell lung cancer, J. Clin. Oncol. 35 (2017) 1395–1402, https://doi.org/10.1200/jco.2016.71.6142.

[17] R.J. Landreneau, D.J. Sugarbaker, M.J. Mack, S.R. Hazelrigg, J.D. Luketich, L. Fetterman, et al., Wedge resection versus lobectomy for stage I (T1 N0 M0) non-small-cell lung cancer, J. Thorac. Cardiovasc. Surg. 113 (1997) 691–698, discussion 8-700.10.1016/s0022-5223(97)70226-698.

[18] J.P. Wisnivesky, E. Halm, M. Bonomi, C. Powell, E. Bagiella, Effectiveness of radiation therapy for elderly patients with unresected stage I and II non-small cell lung cancer, Am. J. Respir. Crit. Care Med. 181 (2010) 264–269, https://doi.org/10.1164/rccm.200907-1064OC.

[19] R. Timmerman, R. Paulus, J. Galvin, J. Michalski, W. Straube, J. Bradley, et al., Stereotactic body radiation therapy for inoperable early stage lung cancer, JAMA 303 (2010) 1070–1076, https://doi.org/10.1001/jama.2010.261.

[20] J.I. Choi, Medically inoperable stage I non-small cell lung cancer: best practices and long-term outcomes, Transl. Lung Cancer Res. 8 (2018) 32–47. https://tlcr.amegroups.com/article/view/22799.

[21] NCCN Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer Version 1.2023- December 22, 2022, NCCN, 2022.

[22] J.L. Warren, C.N. Klabunde, D. Schrag, P.B. Bach, G.F. Riley, Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population, Iv, Med Care 40 (2002) 3–18, https://doi.org/10.1097/01.Mlr.0000020942.47004.03.

[23] Older Persons' Health. Ceneters for Disease Control and Prevention; 2023.

[24] C.D. Corso, H.S. Park, A.C. Moreno, A.W. Kim, B.Y. James, Z.A. Husain, et al., Stage I lung SBRT clinical practice patterns, Am. J. Clin. Oncol. 40 (2017) 358–361.

[25] W. Lim, C.A. Ridge, A.G. Nicholson, S. Mirsadraee, The 8(th) lung cancer TNM classification and clinical staging system: review of the changes and clinical implications, Quant. Imag. Med. Surg. 8 (2018) 709–718, https://doi.org/10.21037/qims.2018.08.02.

[26] P.L. Hebert, L.S. Geiss, E.F. Tierney, M.M. Engelgau, B.P. Yawn, A.M. McBean, Identifying persons with diabetes using Medicare claims data, Am. J. Med. Qual. 14 (1999) 270–277, https://doi.org/10.1177/106286069901400607.

[27] B.A. Young, E. Lin, M. Von Korff, G. Simon, P. Ciechanowski, E.J. Ludman, et al., Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization, Am. J. Manag. Care 14 (2008) 15–23.

[28] G.S. Cooper, B. Virnig, C.N. Klabunde, N. Schussler, J. Freeman, J.L. Warren, Use of SEER-Medicare data for measuring cancer surgery, Iv-43-8, Med Care 40 (2002), https://doi.org/10.1097/00005650-200208001-00006.

[29] B.A. Virnig, J.L. Warren, G.S. Cooper, C.N. Klabunde, N. Schussler, J. Freeman, Studying radiation therapy using SEER-Medicare-linked data, Iv, Med Care 40 (2002) 49–54, https://doi.org/10.1097/00005650-200208001-00007.

[30] J.L. Warren, L.C. Harlan, A. Fahey, B.A. Virnig, J.L. Freeman, C.N. Klabunde, et al., Utility of the SEER-Medicare data to identify chemotherapy use, Iv, Med Care 40 (2002) 55–61, https://doi.org/10.1097/01.Mlr.0000020944.17670. D7.

[31] R.A. Deyo, D.C. Cherkin, M.A. Ciol, Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases, J. Clin. Epidemiol. 45 (1992) 613–619, https://doi.org/10.1016/0895-4356(92)90133-8.

[32] C.N. Klabunde, A.L. Potosky, J.M. Legler, J.L. Warren, Development of a comorbidity index using physician claims data, J. Clin. Epidemiol. 53 (2000) 1258–1267, https://doi.org/10.1016/s0895-4356(00)00256-0.

[33] L.V. van de Poll-Franse, S. Houterman, M.L. Janssen-Heijnen, M.W. Dercksen, J.W. Coebergh, H.R. Haak, Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis, Int. J. Cancer 120 (2007) 1986–1992, https://doi.org/10.1002/ijc.22532.

[34] M.K. Gould, C.E. Munoz-Plaza, E.E. Hahn, J.S. Lee, C. Parry, E. Shen, Comorbidity profiles and their effect on treatment selection and survival among patients with lung cancer, Annals of the American Thoracic Society 14 (2017) 1571–1580, https://doi.org/10.1513/AnnalsATS.201701-030OC.

[35] D. Hernandez, C.Y. Cheng, K. Hernandez-Villafuerte, M. Schlander, Survival and comorbidities in lung cancer patients: evidence from administrative claims data in Germany, Oncol. Res. 30 (2022) 173–185, https://doi.org/10.32604/or.2022.027262.

[36] C.H. Su, W.M. Chen, M. Chen, B.C. Shia, S.Y. Wu, Association of diabetes severity and mortality with lung squamous cell carcinoma, Cancers 14 (2022), https://doi.org/10.3390/cancers14102553.

[37] W. Liu, A. Vyas, C. Escalante, M.A. Weiser, J. Wang, J.M. Geraci, Results of general internal medicine consultations for diabetes mellitus in 283 cancer patients, Am. J. Med. Sci. 333 (2007) 276–279, https://doi.org/10.1097/MAJ.0b013e31805340d4.

[38] L.C. Pinheiro, O. Soroka, L.M. Kern, J.P. Leonard, M.M. Safford, Diabetes care management patterns before and after a cancer diagnosis: a SEER-Medicare matched cohort study, Cancer 126 (2020) 1727–1735, https://doi.org/10.1002/cncr.32728.

[39] J. Zhang, N. Veeramachaneni, Targeting interleukin-1β and inflammation in lung cancer, Biomark Res 10 (2022) 5, https://doi.org/10.1186/s40364-021-00341-5.

[40] D.V. Nguyen, L.C. Shaw, M.B. Grant, Inflammation in the pathogenesis of microvascular complications in diabetes, Front. Endocrinol. 3 (2012) 170, https://doi.org/10.3389/fendo.2012.00170.

[41] D. Yu, W. Zheng, M. Johansson, Q. Lan, Y. Park, E. White, et al., Overall and central obesity and risk of lung cancer: a pooled analysis, J. Natl. Cancer Inst. 110 (2018) 831–842, https://doi.org/10.1093/jnci/djx286.

[42] F.H. Ardesch, R. Ruiter, M. Mulder, L. Lahousse, B.H.C. Stricker, J.C. Kiefte-de Jong, The obesity paradox in lung cancer: associations with body size versus body shape, Front. Oncol. 10 (2020), 591110, https://doi.org/10.3389/fonc.2020.591110.

[43] I. Argirion, S.J. Weinstein, S. Männistö, D. Albanes, A.M. Mondul, Serum insulin, glucose, indices of insulin resistance, and risk of lung cancer, Cancer Epidemiol. Biomarkers Prev. 26 (2017) 1519–1524, https://doi.org/10.1158/1055-9965.Epi-17-0293.

[44] N.E. Kim, E.H. Kang, E. Ha, J.Y. Lee, J.H. Lee, Association of type 2 diabetes mellitus with lung cancer in patients with chronic obstructive pulmonary disease, Front. Med. 10 (2023), 1118863, https://doi.org/10.3389/fmed.2023.1118863.