Original Article

Association between patient medications and postoperative outcomes in early-stage non-small cell lung cancer

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Background: Currently, there is no consensus on how to comprehensively assess comorbidities in lung cancer patients in the clinical setting. Prescription medications may be a preferred comorbidity assessment tool and provide a simple mechanism for predicting postoperative outcomes for lung cancer. We examined the relationship between prescription medications and postoperative outcomes for early-stage non-small cell lung cancer (NSCLC).

Methods: We conducted a retrospective cohort study of patients with clinical stage I NSCLC who underwent surgical resection in the Veterans Health Administration (VHA) between 10/01/2006 and 09/30/2016. Details of all outpatient prescriptions filled by patients within the VHA system from 1-year up to 14 days before surgery were collected. Medications were categorized using the Anatomical Therapeutic Chemical (ATC) Level One classification system. We assessed the association of medications prescribed in the year prior to surgery with postoperative adverse events (composite of death or major complication) at 30 and 90 days following surgery and overall survival (OS).

Results: We included 9,741 veterans in the analysis. The median number of prescription medications filled in the year preceding surgery was 11 (interquartile range: 7–16). In multivariable-adjusted analyses, a higher number of prescription medications was associated with increased risk of 30-day [multivariable-adjusted odds ratio (aOR): 1.016; 95% confidence interval (CI): 1.007–1.026] and 90-day postoperative adverse events (aOR: 1.015; 95% CI: 1.006–1.024) and decreased OS (adjusted hazard ratio: 1.019; 95% CI: 1.014–1.023). Within a subgroup of patients with a high comorbidity burden (Charlson-Deyo Comorbidity Index score of 6–8), a higher number of prescription medications was also associated with reduced OS (P<0.001). Patients prescribed medications from the ATC respiratory system class had elevated risk of postoperative adverse events at 30 days (aOR: 1.255; 95% CI: 1.095–1.439) and 90 days (aOR: 1.254; 95% CI: 1.097–1.434) compared to patients

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without these prescription medications. Significantly increased odds for 90-day postoperative adverse events were observed with each additional prescription medication from the ATC respiratory (aOR: 1.057; 95% CI: 1.027–1.088) and nervous system (aOR: 1.035; 95% CI: 1.005–1.066) classes.

Conclusions: The number of medications prescribed preoperatively is associated with short- and long-term postoperative outcomes for early-stage NSCLC, even when adjusting for several covariates including age and comorbidity burden. Patients prescribed a higher number of medications acting primarily on the respiratory and nervous systems are at elevated risk for postoperative adverse events after curative-intent resection. Prescription medications may be a reliable tool to assess comorbidities and perioperative risk for patients with NSCLC.

Keywords: Medications; lung cancer; non-small cell lung cancer (NSCLC); outcomes; lung cancer surgery

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Highlight box

Key findings

- In a retrospective analysis of 9,741 United States veterans with clinical stage I non-small cell lung cancer (NSCLC), a higher number of prescription medications was associated with increased risk of postoperative adverse events and reduced overall survival, even when adjusting for several covariates including age and comorbidity burden.
- We observed an additional 5.7% and 3.5% risk of postoperative adverse events at 90 days with each additional prescription medication acting primarily on the respiratory and nervous systems, respectively.

What is known and what is new?

- It is well-recognized that an accurate comorbidity assessment is essential in patients with early-stage NSCLC to guide candidacy for surgery versus stereotactic body radiation therapy and predict prognosis. However, there is no consensus on how to comprehensively assess comorbidities in patients with NSCLC using real-time data.
- Our analysis newly demonstrates that detailed, patient-level medication assessments can inform risk of adverse short- and long-term outcomes after curative-intent resection of early-stage NSCLC. It appears that patients prescribed a higher number of medications acting primarily on the respiratory and nervous systems are at elevated risk for postoperative adverse events.

What is the implication, and what should change now?

- Based on these findings, prescription medications may be a potential tool to assess comorbidities and their associated perioperative risks for patients with early-stage NSCLC.
- Medication-based risk prediction models could enhance precision lung cancer care by helping to inform prognosis, guide treatment selection, and mitigate adverse events.

Introduction

Lung cancer is the leading cause of cancer-related mortality in the United States (US) (1). It is estimated that 238,340 new cases and 127,070 lung cancer-related deaths occurred nationwide in 2023 (1). The annual national cost of lung cancer care has been estimated to exceed $20 billion and is projected to increase further over the next decade (2). Hence, evidence-based management of lung cancer should be a national priority for optimization of outcomes and resource utilization.

Chronic health conditions are common in older adults, especially in those with lung cancer, and are expected to increase in prevalence with the aging population (3,4). It has previously been shown that lung cancer survivors have the highest comorbidity burden compared to those with other cancers, with greater than 50% of survivors experiencing severe comorbidity burden (4). Compared to the civilian population, US veterans have higher rates of chronic diseases including diabetes, cardiovascular disease, chronic obstructive pulmonary disease (COPD), and cancer, which may be attributable to unique service-related risk factors such as Agent Orange exposure and high rates of tobacco use (5-10). In particular, approximately 8,000 new lung cancers are diagnosed annually in the Veterans Health Administration (VHA) (11).

An accurate comorbidity assessment is essential in patients with early-stage non-small cell lung cancer (NSCLC) to guide candidacy for surgery versus stereotactic body radiation therapy, inform of potential treatment-related risks and

adverse events, and predict prognosis. Furthermore, comorbidities, such as COPD and cardiovascular disease, have been shown to influence long-term survival in lung cancer (12-15). Despite the importance of accurate comorbidity assessments, there is no consensus on how to comprehensively assess comorbidities in patients with NSCLC using real-time data. Established comorbidity indices, such as the Charlson Comorbidity Index (CCI) and the Elixhauser Comorbidity Index (ECI), often have limited applicability in clinical settings due to frequently incomplete documentation of comorbidities in modern electronic health records (EHRs) (16-18). These comorbidity indices rely upon administrative codes used for hospital billing, lack specificity, may not be appropriately weighted, and are calculated retrospectively. Furthermore, administrative codes may not reflect disease severity, are infrequently updated, can be discordant between clinicians, and are influenced by hospital billing practices. Hence, there is an unmet need for reliable and real-time comorbidity assessment tools that can accurately assess comorbidity burden and predict outcomes for early-stage NSCLC.

Prescription medications are readily available in EHRs and may serve as a more accurate and up-to-date comorbidity measure for predicting surgical outcomes for NSCLC. Multiple prior studies have demonstrated that perioperative use of bronchodilators can influence postoperative outcomes in lung cancer patients with COPD (19-23). Hence, we hypothesized that both the number and type of prescription medications are associated with postoperative outcomes in patients undergoing definitive resection for NSCLC. We tested this hypothesis in a comprehensive, unique cohort of US veterans diagnosed with early-stage NSCLC. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-803/rc).

Methods

We conducted a retrospective cohort study of patients diagnosed with clinical stage I NSCLC who underwent curative-intent resection in the VHA between 10/01/2006 and 09/30/2016. Data elements were retrieved using the VHA Informatics and Computing Infrastructure (VINCI) system, which contains clinical and administrative data from multiple national data repositories in the Corporate Data Warehouse (CDW), including CDW-Oncology Raw and Veterans Affairs Surgical Quality Improvement Program (VASQIP) (24). To ensure maximal data capture, this unique dataset was compiled by a team of dedicated abstractors across 24 months using a combination of manual chart reviews and natural language processing techniques. We identified patients with a diagnosis of NSCLC through query of International Classification of Diseases (ICD) for Oncology, third edition codes, and confirmed procedures using ICD-9, ICD-10, or Current Procedural Terminology (CPT) codes. We included adults (age 18 or older) who were diagnosed with clinical stage I (tumors ≤5 cm, node-negative disease) disease, as defined by the American Joint Committee on Cancer (7^{th} edition), and underwent curative-intent surgical resection. Patients who had a missing diagnosis date, received neoadjuvant treatment, or presented with a recurrent cancer were excluded from this study.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the St. Louis VHA's Research and Development Committee (#1214632), and individual consent for this retrospective analysis was waived.

As previously described by our group and other authors, medication data was obtained for all patients using the CDW Pharmacy Outpatient database, which contains detailed prescription medication information including date of issue, date of fill, number of refills prescribed, administration route, dose prescribed, and administration frequency (19,25). Data from all outpatient prescriptions filled by patients within the VHA system from one-year up to fourteen days prior to surgery were collected. This timeframe was selected as medications prescribed greater than one year before surgery were considered to less accurately reflect a patient's overall health status at the time of surgery. We categorized prescription medications using the World Health Organization Anatomical Therapeutic Chemical (ATC) Level One classification system, which is considered the gold standard for drug utilization monitoring and research (26). In the ATC classification system, medications are divided into groups at five different levels according to the organ or body system they effect as well as their therapeutic, pharmacological, and chemical properties. The Level One classification system is the broadest level and consists of fourteen anatomical or pharmacological groups (*Table 1*). Two authors (S.T., C.P.) independently categorized medications into ATC Level One classes. A co-senior author (M.W.S.) then manually reviewed both compiled lists and adjudicated decisions regarding medication classification in discrepant cases.

Table 1 World Health Organization ATC Level One classification system

ATC Level One classification	Example medications
A: alimentary tract and metabolism	Ondansetron, omeprazole, metformin
B: blood and blood forming organs	Warfarin, apixaban, clopidogrel
C: cardiovascular system	Metoprolol, furosemide, hydralazine
D: dermatologics	Griseofulvin, benzoyl peroxide
G: genitourinary system and sex hormones	Testosterone, finasteride, sildenafil
H: systemic hormonal preparations	Levothyroxine, fludrocortisone
J: anti-infective for systemic use	Doxycycline, amoxicillin
L: antineoplastic and immunomodulating agents	Tacrolimus, infliximab, doxorubicin
M: musculoskeletal system	Methocarbamol, baclofen
N: nervous system	Oxycodone, levodopa, haloperidol
P: antiparasitic products, insecticides, and repellents	Hydroxychloroquine, praziquantel
R: respiratory system	Salmeterol, fluticasone, tiotropium
S: sensory organs	Pilocarpine, latanoprost
V: various	Sevelamer, mesna, deferoxamine

Table contents were obtained using publicly available information from the World Health Organization (https://www.whocc.no/atc_ddd_index/) (26). ATC, anatomical therapeutic chemical.

Several patient-, tumor-, and treatment-related covariates were abstracted from the CDW system. Comorbidities were measured using the composite Charlson-Deyo Comorbidity Index, which was calculated using ICD-9 and ICD-10 codes present from 5 years prior to 1 month after surgery (27). We extracted oncologic and treatment-related covariates for each patient, which included tumor size, grade, histology, year of operation, hospital case load (defined as the volume of lung cancer cases treated at a specific facility in the year prior to surgery), surgical approach, operation type (lobectomy, segmentectomy, wedge resection, or pneumonectomy), lymph node assessment, and pathologic stage.

Statistical analysis

The primary outcome of the study was postoperative adverse events at 30 and 90 days following surgery. This composite endpoint was generated as a binary variable (yes/no) consisting of perioperative mortality and/or the presence of major postoperative complications (defined as a diagnosis of a pneumonia, empyema, myocardial infarction, respiratory failure, renal failure, or stroke within 30 days after surgery). Postoperative complications were identified using the VASQIP database, a reliable and validated method for detection of postoperative adverse events, as well as ICD-9 and ICD-10 diagnosis codes (19,28,29). Multivariable logistic regression models adjusting for patient sociodemographic, comorbidity, tumor, and operative characteristics were used to assess the relationship between the number of prescription medications, ATC Level One medication classes, and postoperative adverse events. Our secondary outcome was overall survival (OS), defined as the time between date of surgery and all-cause mortality. Date of death was determined from the VHA Vital Status Files. OS was censored at the completion of the study's follow-up period (05/01/2020). OS was presented using the Kaplan-Meier method and assessed using multivariable Cox proportional hazards model.

Model performance with and without inclusion of patient comorbidities was evaluated using the Akaike information criterion (AIC) statistic and c-statistic. The AIC is an estimator of prediction error and the relative quality of statistical models for a given dataset. The c-statistic represents the area under the receiver operator characteristic curve and assesses model discrimination. Model performance for the outcome of 30-day postoperative adverse events with and without comorbidities were as follows: c-statistic with comorbidities is 0.672, and c-statistic without comorbidities

is 0.654. The AIC with comorbidities is 7,242 and without comorbidities is 7,327. As shown in Table S1, this trend was also observed when examining model performance for the outcomes of 90-day postoperative adverse events and OS. Both parameters suggested better discrimination and model fit with the inclusion of patient comorbidities for the primary and secondary outcomes.

Descriptive statistics were reported as means with standard deviations (SD) for continuous variables and as frequencies with proportions for categorical variables. Missing data points were minimal and categorized as unknown. All statistical tests were two-sided, with P values less than 0.05 deemed statistically significant. Analyses were conducted in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

In total, 9,741 veterans met inclusion criteria and were included in the analysis. The median age of the study cohort was 67.0 [interquartile range (IQR): 62.3–73.0] years. Most veterans were male (n=9,383, 96.3%), of White race (n=8,060, 82.7%), were smoking at the time of surgery (n=5,697, 58.5%), and underwent lobectomy (n=6,907, 70.9%). The mean Charlson-Deyo Comorbidity Index score was 6.89 (SD: 2.22). Detailed characteristics of the study cohort are shown in *Table 2* (19). Major postoperative complications occurred in 1,351 (13.9%) veterans and occurred most frequently following lobectomy (n=1,047/6,907, 15.2%). The rate of major postoperative complications stratified by operation type is detailed in Table S2. The rate of postoperative mortality at 30 days was 2.2% (n=196). Deaths occurred in 5,760 (59.1%) veterans over a median follow-up of 6.1 (IQR: 2.5–11.4) years.

The median number of prescription medications filled in the year prior to surgery was 11 (IQR: 7–16). A median of 5 (IQR: 4–7) unique ATC Level One classes were represented among these prescription medications. As detailed in *Table 3*, 8,050 (82.6%), 7,468 (76.7%), and 6,289 (64.6%) veterans were prescribed at least one medication from the ATC cardiovascular, nervous, and respiratory system classes, respectively. In a multivariable linear model, a higher number of prescription medications was associated with younger age, higher Charlson-Deyo Comorbidity Index score, increased body mass index, female sex, black race, prior tobacco use, living closer to the treatment facility, high area deprivation index, squamous cell carcinoma, and sublobar resection (all P<0.05).

In multivariable analyses, a higher number of prescription medications was associated with increased risk of postoperative adverse events at 30 days [multivariable-adjusted odds ratio (aOR), 1.016; 95% confidence interval (CI): 1.007–1.026] and 90 days (aOR: 1.015; 95% CI: 1.006–1.024). A higher number of prescription medications was also associated with increased risk of mortality [multivariable-adjusted hazard ratio (aHR), 1.019; 95% CI: 1.014–1.023]. Within a subgroup of patients with a high comorbidity burden (Charlson-Deyo Comorbidity Index score of 6–8), a higher number of prescription medications was also associated with increased risk of mortality (P<0.001; *Figure 1*).

Inclusion of each ATC Level One medication class as a covariate (yes/no) in the multivariable regression model revealed that veterans prescribed medications from the ATC respiratory system class had increased odds of 30-day (aOR: 1.255; 95% CI: 1.095–1.439; *Figure 2A*) and 90-day (aOR: 1.254; 95% CI: 1.097–1.434; *Figure 2B*) postoperative adverse events compared to patients not prescribed these medications. Veterans prescribed medications from the ATC anti-infective for systemic use class had decreased odds of 30-day (aOR: 0.856; 95% CI: 0.753–0.972) and 90-day (aOR: 0.860; 95% CI: 0.759–0.975) postoperative adverse events compared to patients not prescribed these medications. Veterans prescribed medications from the ATC blood and blood forming organs (aHR, 1.084; 95% CI: 1.020–1.152), systemic hormonal preparations (aHR, 1.135; 95% CI: 1.063–1.211), nervous system (aHR, 1.114; 95% CI: 1.040–1.194), and respiratory system (aHR, 1.073; 95% CI: 1.009–1.140) classes had higher risk of mortality in the multivariable-adjusted model (*Figure 3*).

Each additional prescription medication from the ATC respiratory system class was associated with a 6.2% increased risk for postoperative adverse events at 30 days (aOR: 1.062; 95% CI: 1.031–1.093; *Table 4*). Increased odds for postoperative adverse events at 90 days were observed with each additional prescription medication from the ATC respiratory (aOR: 1.057; 95% CI: 1.027–1.088) and nervous system (aOR: 1.035; 95% CI: 1.005–1.066) classes. Compared to patients not prescribed medications from these drug classes, there was elevated risk for mortality with each additional medication prescribed from the ATC alimentary tract and metabolism (aHR, 1.034; 95% CI: 1.007–1.061), cardiovascular (aHR, 1.026; 95% CI: 1.009–1.042), systemic hormonal preparations (aHR, 1.072; 95% CI: 1.016–1.130), antineoplastic and immunomodulating agents (aHR, 1.108; 95% CI: 1.013–1.212), nervous (aHR, 1.028; 95% CI: 1.014–1.042), and respiratory (aHR, 1.017;

Table 2 Characteristics of the study cohort

Patient characteristics	Study cohort, No. (%, n=9,741)
Age (years), mean (SD)	67.61 (7.89)
Sex, n (%)	
Female	358 (3.68)
Male	9,383 (96.32)
Race, n (%)	
Black	1,457 (14.96)
Other	131 (1.34)
White	8,060 (82.74)
Unknown	93 (0.95)
Body mass index (kg/m^2), n (%)	
<18.5	307 (3.19)
18.5–24.9	3,276 (34.04)
25–29.9	3,464 (36.03)
30–34.9	1,833 (19.07)
≥35	734 (7.63)
Smoking status (at time of surgery), n (%)	
Current	5,697 (58.48)
Former	3,912 (40.16)
Never	132 (1.36)
Charlson-Deyo Comorbidity Index, median (IQR)	6.89 (2.22)
Distance from hospital (m), n (%)	
≤10	2,131 (21.88)
11–50	3,929 (40.33)
>50	3,681 (37.79)
Area deprivation index, n (%)	
Quartile 1 (least deprived)	2,357 (24.29)
Quartile 2	2,459 (25.34)
Quartile 3	2,523 (26.00)
Quartile 4 (most deprived)	2,365 (24.37)
Histology, n (%)	
Adenocarcinoma	5,192 (53.30)
Squamous cell carcinoma	3,292 (33.80)
Other	1,257 (12.90)
Grade, n (%)	
I	1,218 (13.28)
II	4,827 (52.64)
III	2,991 (32.62)
IV	133 (1.45)
Tumor size (mm), n (%)	
≤10	890 (9.14)
11–20	3,922 (40.26)
21–30	2,693 (27.65)
31–40	1,501 (15.41)
41–50	729 (7.48)
Delayed operation (>12 weeks), n (%)	3,045 (31.26)
Surgical approach, n (%)	
Thoracotomy	5,686 (58.53)
Minimally invasive	4,028 (41.47)
Resection type, n (%)	
Lobectomy	6,907 (70.91)
Pneumonectomy	155 (1.59)
Segmentectomy	540 (5.54)
Wedge resection	2,139 (21.96)
Lymph node sampling, n (%)	
<3 N2 and/or <1 N1	7,184 (73.75)
≥3 N2 and ≥1 N1	2,557 (26.25)
Surgical margin, n (%)	
R0	9,321 (96.71)
R1/R2	317 (3.29)
Pathologic upstage, n (%)	
No	8,487 (87.13)
Yes	1,254 (12.87)

Table adapted with permission from AME Publishing Company (19).
SD, standard deviation; IQR, interquartile range.

95% CI: 1.004–1.031) system classes.

Discussion

The presence of comorbid conditions informs treatment selection and prognosis in veterans with early-stage NSCLC. Reliable comorbidity assessment is a critical component of high-quality lung cancer care. Over the last three decades, several comorbidity indices have been developed for prediction of morbidity and mortality. The commonly cited CCI was first developed as a weighted comorbidity index to predict risk of mortality and has since been adapted by integrating ICD and CPT codes (17,30,31). Similarly,

Table 3 Medications prescribed in the year prior to surgery stratified by Anatomical Therapeutic Chemical Level One Class

Anatomical Therapeutic Chemical Level One Class	Total number of patients prescribed at least one medication (%, n=9,741)	Mean number of prescription medications per patient (standard deviation)
A: alimentary tract and metabolism	6,254 (64.2)	1.17 (1.2)
B: blood and blood forming organs	3,160 (32.4)	0.43 (0.7)
C: cardiovascular system	8,050 (82.6)	2.56 (2.0)
D: dermatologics	3,359 (34.5)	0.59 (1.0)
G: genitourinary system and sex hormones	3,861 (39.6)	0.57 (0.8)
H: systemic hormonal preparations	2,281 (23.4)	0.27 (0.5)
J: anti-infective for systemic use	4,899 (50.3)	1.02 (1.4)
L: antineoplastic and immunomodulating agents	574 (5.9)	0.07 (0.3)
M: musculoskeletal system	3,698 (38.0)	0.53 (0.8)
N: nervous system	7,468 (76.7)	2.50 (2.3)
P: antiparasitic products, insecticides, and repellents	101 (1.0)	0.01 (0.1)
R: respiratory system	6,289 (64.6)	2.02 (2.2)
S: sensory organs	999 (10.3)	0.17 (0.6)
V: various	1,669 (17.1)	0.17 (0.4)

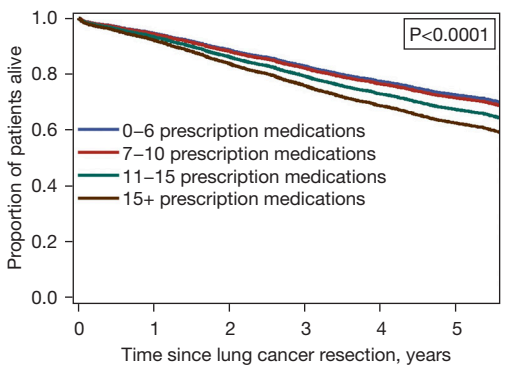

Figure 1 Adjusted Kaplan-Meier survival analysis of patients with a Charlson-Deyo Comorbidity Index score of 6–8.

the ECI includes 30 comorbidities and was developed as a comorbidity measure for use in administrative database research (18). While these comorbidity indices have been frequently used in retrospective outcomes research, they are rarely used to make treatment decisions and have not been readily integrated into EHR platforms or patient-centered oncology care models. Established comorbidity indices rely on the accurate collection of ICD and CPT codes, which are primarily used by hospitals for reimbursement and to report diagnoses, procedures, and services rendered. As comorbidities are often underreported in hospital administrative data, this may be an inaccurate method to quantify comorbidity burden in cancer patients (16). Additionally, an updated list of administrative codes is usually unavailable at the time of a patient's clinic visit as these data elements are coded by abstractors at various times. Hence, there are significant limitations to the use of these comorbidity assessment tools for patients with NSCLC.

Prescription medications may be a reliable, easy-to-use, and real-time comorbidity measurement tool for patients with NSCLC. In contrast to administrative codes, medication lists are readily accessible for each patient in modern EHR platforms and are reconciled with each clinical encounter, providing a real-time reflection of an individual's current comorbidity status. Additionally, administrative data obtained for coding and reimbursement of clinical encounters does not accurately represent a patient's true comorbidity burden and has limited ability to determine disease severity or control within a specific diagnosis (*Table 5*). Review of prescription medications can provide more detailed information regarding comorbidity severity and disease control (e.g., a single prescribed bronchodilator for well-controlled COPD compared to multiple steroid prescriptions for recurrent COPD exacerbations). Furthermore, prescription medications are

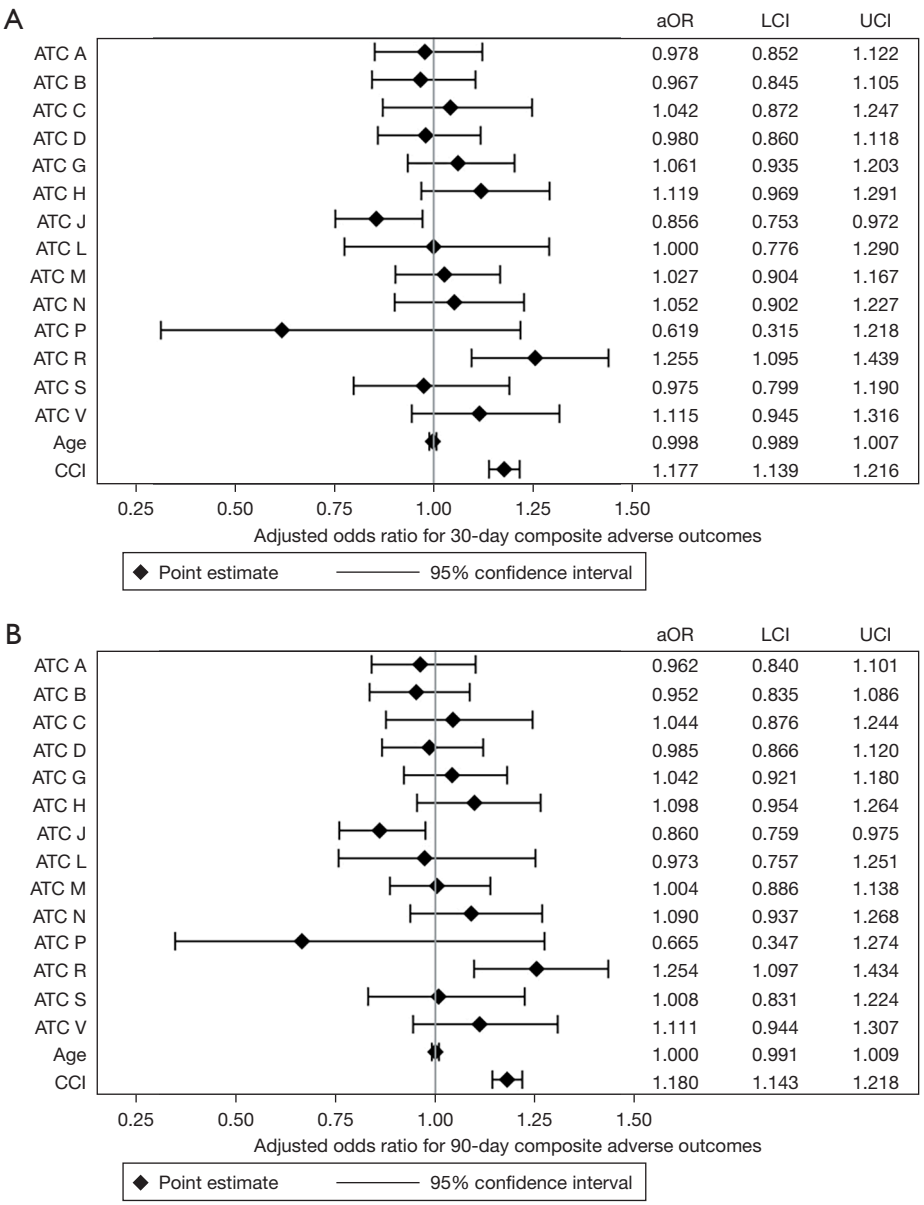

Figure 2 Association between Anatomical Therapeutic Chemical Level One Class (yes/no) and postoperative adverse outcomes at thirty (A) and ninety days (B) following surgery. ATC, Anatomical Therapeutic Chemical; CCI, Charlson-Deyo Comorbidity Index; aOR, adjusted odds ratio; LCI, lower limit of 95% confidence interval; UCI, upper limit of 95% confidence interval.

patient-specific and can highlight the distinct health factors that may influence an individual's outcomes after treatment for NSCLC.

Our analysis of a large national cohort of veterans demonstrates that detailed, patient-level medication assessments can inform risk of adverse short- and long-term outcomes after resection of early-stage NSCLC. We found that a higher number of prescription medications was associated with increased risk of postoperative adverse events and reduced OS, even when adjusting for several covariates including age and comorbidity burden. It appears that patients prescribed a higher number of medications acting primarily on the respiratory and nervous systems are at elevated risk for postoperative adverse events. We observed an additional 5.7% and 3.5% risk of postoperative adverse events at 90 days post-surgery with each additional

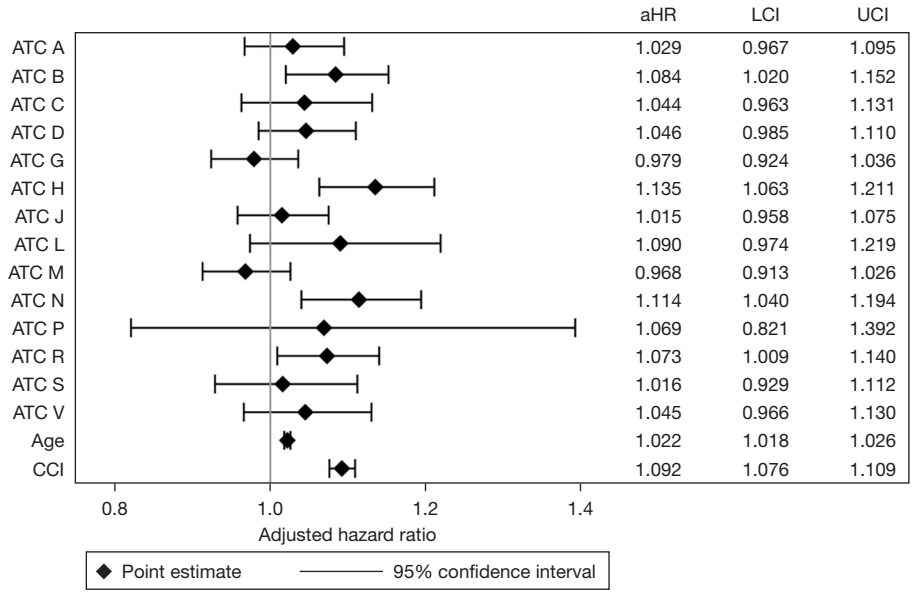

Figure 3 Association between ATC Level One Class (yes/no) and overall survival. ATC, Anatomical Therapeutic Chemical; CCI, Charlson-Deyo Comorbidity Index; aHR, adjusted hazard ratio; LCI, lower limit of 95% confidence interval; UCI, upper limit of 95% confidence interval.

Table 4 Association between the number of prescription medications from an ATC Level One class, postoperative adverse events, and overall survival

ATC class	30-day postoperative adverse events	90-day postoperative adverse events	Overall survival
A	0.977 (0.923–1.034)	0.975 (0.922–1.031)	1.034 (1.007–1.061)*
B	0.993 (0.909–1.085)	0.984 (0.902–1.073)	1.027 (0.987–1.069)
C	1.014 (0.978–1.050)	1.012 (0.978–1.048)	1.026 (1.009–1.042)*
D	0.993 (0.933–1.058)	0.996 (0.936–1.059)	1.006 (0.979–1.035)
G	1.025 (0.951–1.104)	1.008 (0.937–1.085)	0.969 (0.936–1.003)
H	1.041 (0.924–1.171)	1.021 (0.908–1.147)	1.072 (1.016–1.130)*
J	0.965 (0.921–1.012)	0.967 (0.923–1.013)	1.007 (0.986–1.028)
L	1.006 (0.817–1.239)	1.000 (0.815–1.226)	1.108 (1.013–1.212)*
M	1.009 (0.933–1.092)	0.998 (0.924–1.078)	0.979 (0.944–1.016)
N	1.029 (0.998–1.060)	1.035 (1.005–1.066)*	1.028 (1.014–1.042)*
P	0.625 (0.318–1.229)	0.666 (0.348–1.275)	1.097 (0.845–1.424)
R	1.062 (1.031–1.093)*	1.057 (1.027–1.088)*	1.017 (1.004–1.031)*
S	0.971 (0.879–1.073)	0.986 (0.896–1.086)	1.013 (0.970–1.057)
V	1.126 (0.950–1.334)	1.121 (0.948–1.324)	1.018 (0.939–1.103)

Data are reported as adjusted odds ratio or hazard ratio with 95% confidence interval. *, statistical significance. ATC, Anatomical Therapeutic Chemical.

prescription medications from the ATC respiratory and nervous system classes, respectively. These two ATC classes include medications that are commonly prescribed to older adults, such as bronchodilators for COPD, analgesics for chronic pain, and psychotropic medications. In this study, approximately 65% and 77% of patients were prescribed

Table 5 Representative patient medical records with discrepancies between provider-documented active health problems and prescription medications

Health problem list	Prescription medications
Hypertension	Aspirin 81 mg PO daily
Chronic obstructive pulmonary disease	Albuterol 90 mcg/actuation inhaler, inhale 2 puffs every 6 hours PRN
Non-small cell lung cancer	Diltiazem XR 180 mg PO daily
Chronic pain	Lisinopril 10 mg PO daily
Colon cancer screening	Loratadine 10 mg PO daily
Allergic rhinitis	Metoprolol succinate ER 50 mg PO daily
Congestive heart failure	Oxycodone 5 mg PO QID PRN
Encounter for tetanus, diphtheria, pertussis (Tdap) vaccine	Tiotropium bromide 2.5 mcg/actuation inhaler, inhale 2 puffs daily
History of asthma	
History of snake bite	
Diabetes mellitus	
History of motor vehicle accident	
Generalized abdominal pain	
Metacarpal fracture of the hand	
History of anxiety	
Cellulitis	
Vertigo	
Obesity	
Hypothyroidism	
History of seizure	

PO, per os; PRN, as needed; XR/ER, extended-release; QID, four times a day.

medications from the ATC respiratory and nervous system classes, respectively. These findings build on prior analyses from our group which revealed that the perioperative use of opiates and inhaled COPD medications are associated with increased risk of adverse outcomes after pulmonary resection (19,32).

Based on these findings, prescription medications may be a potential tool to assess comorbidities and their associated perioperative risks for patients with early-stage NSCLC. The potential association between prescription medications and patient outcomes for other cancer types also warrants special attention and should be explored in future studies. Additional research efforts should also target defining the relationship between prescription medications, comorbid disease diagnoses, and cancer treatment allocation. If larger studies validate these findings, a predictive model using prescription medications for perioperative risk stratification could be adopted into clinical practice given the automated integration of medication lists into EHRs for real-time comorbidity assessments. Medication-based risk prediction models could enhance precision lung cancer care by helping to inform prognosis, guide treatment selection, and mitigate adverse events.

As previously described by our group, a limitation of this work is that the number of prescription medications consists only of the outpatient prescriptions that were filled by the patient before surgery and did not include inpatient medications or prescriptions from other healthcare systems outside of the VHA (19). Additionally, we were unable to assess medication adherence as the analysis was completed retrospectively. Since the study population primarily consisted of male US veterans, further research is also needed to determine if these findings apply to the broader population, including women. While we examined

the frequencies of several common medical comorbidities and major complications after lung cancer resection, we were limited in our ability to account for all potential patient comorbidities (e.g., nutritional status, anemia) and postoperative complications (e.g., atrial arrhythmias, unexpected return to the operating room) in the analysis. Despite these limitations, we believe that this study has several strengths. Specifically, it presents data from a uniquely compiled, nationally representative dataset which contains a comprehensive list of covariates and minimal missing data elements. Additionally, we believe that VHA pharmacy data is ideally suited for this analysis as it is recognized that veterans have more equitable access to care, compared to patients with other insurance types, and low rates of cost-related medication non-adherence (33). Medications, procedures, and provider visits are available to veterans with often minimal or no copayments (34-36). Therefore, assessment of prescription medications is considered reliable in the VHA population (19,25,37,38).

Conclusions

Collectively, our findings suggest that prescription medications may be a reliable tool to assess comorbidities and perioperative risk for patients with NSCLC. In this study, patients prescribed a higher number of medications acting primarily on the respiratory and nervous systems appear to be at elevated risk for postoperative adverse events after curative-intent resection. Routine assessment of prescription medications prior to elective surgery may help identify lung cancer patients who may benefit from additional medical optimization prior to elective surgical resection. Future development of medication-based risk prediction models could enhance precision lung cancer care by helping to inform prognosis, guide treatment selection, and mitigate adverse events.

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Footnote

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