Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-23-1273

Reviewer A

This is an interesting study concerning COPD medication and survival.

However, those relation were already well-known contents and we should be careful for those with COPD.

Comment 1: What next should we do based on the study, what kind of future perspective be stated?

Reply 1: Thank you for your suggestion to expand on this. We have modified our "Discussion" section to include the following paragraph.

Changes in the text:

While not included in this analysis, it is important to note that the association between prescription medications and overall survival may be present in other disease states as well. Our group is exploring these associations in prostate cancer and multiple myeloma. Additionally, future research should investigate the utility of prescription medications as a comorbidity measure through direct comparison to other routinely used comorbidity indices, such as the Charlson comorbidity index. (Lines 391-396)

Reviewer B

The study was well conducted. Authors stratified 3 groups of patients according to the value of predicted postoperative FEV1. They demonstrated a correlation between inhaled Treatment and postoperative outcomes (more prolonged hospital stay and major postoperative complications). This correlation was observed in all groups even in patients with predicted postoperative FEV1 > 80%.

Limits and comments:

Comment 2: In the method chapter, the authors specified they had considering all criteria around oncologic lung surgery. However there is no data on the surgical procedure itself. Nevertheless it is well known that mortality or complications are greater after pneumonectomy than lobectomy and even greater after segmentectomy. It is the main criticism for this study whose primary outcome was overall survival; secondary outcomes were 30-day mortality, 30-day readmission, prolonged hospital length of stay (defined as 14 days or greater), presence of a major complication, and disease-free survival well described. A short chapter dedicated to surgical aspects of the cohort would have been interesting in this

analysis. In fact the results obtained in this study should be interpreted with caution due to these confounding factors impacting morbidity and mortality.

Reply 2: Thank you for this suggestion. We have included the two supplementary tables in the final paper (lines 518-538) to address the effect of surgical treatments on our results. Additionally, we have now clarified that our primary multivariable analysis adjusts for the type of operation and surgical approach. As seen in Supplementary Table 1, 6,907 (70.9%) veterans underwent lobectomy, 155 (1.6%) underwent pneumonectomy, 540 (5.5%) underwent segmentectomy, and 2,139 (22%) underwent wedge resection. We then created subgroups based on operation received and ran multivariate analysis to determine the association between the number of prescribed inhaled COPD medications and short- and long-term outcomes, stratified by operation type. Results of this analysis are shown in Supplementary Table 2.

Supplementary Table 1: Characteristics of the Veterans Health Administration Study Population

Characteristic	**Study cohort, No. (%) (N=9,741)**
Age, mean (standard deviation)	67.61 (7.89)
Sex	
Female	358 (3.68)
Male	9,383 (96.32)
Race	
Black	1,457 (14.96)
Other	131 (1.34)
Unknown	93 (0.95)
White	8,060 (82.74)
Body mass index	
<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)	
Current	5,697 (58.48)
Former	3,912 (40.16)
Never	132 (1.36)
Charlson Comorbidity Index score, median (interquartile range)	6.89 (2.22)
Distance from hospital (miles)	
<=10	2,131 (21.88)
11-50	3,929 (40.33)
50+	3,681 (37.79)
Area Deprivation Index	
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	
Adenocarcinoma	5,192 (53.30)

Squamous cell carcinoma	3,292 (33.80)
Other	1,257 (12.90)
Grade	
I	1,218 (13.28)
II	4,827 (52.64)
III	2,991 (32.62)
IV	133 (1.45)
Tumor size (mm)	
<=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)	3,045 (31.26)
Incision type	
Thoracotomy	5,686 (58.53)
Minimally invasive	4,028 (41.47)
Resection type	
Lobectomy	6,907 (70.91)
Pneumonectomy	155 (1.59)
Segmentectomy	540 (5.54)
Wedge Resection	2,139 (21.96)
Nodal sampling adequacy	
<3 N2 and/or <1 N1	7,184 (73.75)
≥3 N2 and ≥1 N1	2,557 (26.25)
Margin	
R0	9,321 (96.71)
R1+	317 (3.29)
Pathologic upstage	
No upstage present	8,487 (87.13)
Upstage present	1,254 (12.87)

Supplementary Table 2: Association (adjusted odds ratios) between the number of prescribed inhaled chronic obstructive pulmonary disease medications and short- and long-term outcomes, stratified by operation type. ***Sublobar resection includes segmentectomy and wedge resection.***

Outcome	**Open Lobectomy (N=4,298)**	**Video-assisted Thoracoscopic Lobectomy (N=2,592)**	**Open Sublobar Resection (N=1,237)**	**Video-assisted Thoracoscopic Sublobar Resection (N=1,433)**
30-day Mortality	1.09 (0.95,1.25)	1.25 (1.03,1.53)	0.95 (0.77,1.18)	1.03 (0.85,1.24)
30-day Readmission	1.05 (0.97,1.13)	1.00 (0.90,1.17)	1.04 (0.91,1.19)	0.92 (0.80,1.04)
Prolonged Hospital Stay	1.11 (1.05,1.18)	1.08 (0.99,1.19)	1.15 (1.03,1.29)	1.15 (1.02,1.30)
30-day Major Complications	1.12 (1.05,1.18)	1.14 (1.05,1.24)	1.16 (1.03,1.30)	1.09 (0.96,1.25)

90- day Mortality	1.10 (0.99,1.22)	1.19 (1.02, 1.40)	0.92 (0.70,1.21)	1.03 (0.85,1.24)
Overall Survival	1.06 (1.03,1.09)	1.07 (1.03,1.11)	1.05 (0.99,1.10)	1.07 (1.02,1.11)
Disease-free Survival	1.04 (0.99,1.09)	0.99 (0.93,1.05)	1.04 (0.97,1.12)	1.03 (0.96,1.10)

Changes in the text:

Additional characteristics of the study cohort are detailed in Supplementary Table 1. (Line 256)

In the study cohort, 6,907 (70.9%) veterans underwent lobectomy, 155 (1.6%) underwent pneumonectomy, 540 (5.5%) underwent segmentectomy, and 2,139 (22%) underwent wedge resection. (Lines 261-263).

While our primary multivariable analysis adjusted for the type of operation and surgical approach used, we also assessed the relationship between the number of prescription medications and outcomes based on the operation type received. The detailed results of this analysis are listed in Supplementary Table 2. The results of the primary and secondary outcomes were mostly consistent among subgroups despite different operation types being performed. A higher number of medications was associated with worse overall survival in patients undergoing open lobectomy, VATS lobectomy, and VATS sublobar (segmentectomy or wedge) resection. (Lines 294-300).

Comment 3: Moreover, it is a retrospective study that used veteran database including 9741 patients, only men. That is not representative of the global population of patients who undergone surgery for lung cancer.

Reply 3: Thank you for the comment. This has now been addressed in the "Discussion" section of the manuscript. We agree that it is an important limitation of this study.

Changes in the text: There are some limitations to this study. First, our study population consists of United States veterans who were primarily men. Further research is warranted to validate if our findings translate to the population outside of the VHA, including women. (Lines 373-375)

Comment 4: why do the authors only consider 30-day mortality rather than 90-day mortality, well known to have a more accurate aspect of death after surgical procedure in thoracic oncology.

Reply 4: Thank you for this suggestion. We have now included 90-day mortality in our analyses for the overall cohort and subgroups. Please see below for complete analysis. There continues to be an association between the number of prescription drugs and 90-day mortality in the overall study population, those with FEV_1 >80%, and those prescribed SABAs.

Odds ratios for 90-day mortality:

Total number of COPD drugs: 1.088 (1.013,1.170)

Total number of COPD drugs by FEV_1:

>80% = 1.166 (1.019,1.333);

50-79% = 1.054 (0.955,1.164);

<50% = 0.832 (0.663,1.043)

By COPD medication classification:

SABA = 1.527 (1.120,2.083);

SAMA = 0.941 (0.684, 1.296);

LABA = 0.700 (0.464,1.057);

LAMA = 1.052 (0.710,1.559);

ICS = 1.261 (0.855,1.859)

Changes in the text:

We have added the following sentences to the text:

In this cohort, a higher number of inhaled COPD medications was associated with increased 90-day mortality (aOR, 95% CI: 1.088, 1.013-1.170) and decreased overall survival (adjusted hazard ratio [aHR], 95% CI: 1.061, 1.042-1.080) [line 290].

In a subset of patients with FEV1 ≥80% predicted, a greater number of inhaled COPD medications was associated with increased 30-day mortality (aOR, 95% CI: 1.265, 1.062-1.505), increased 90-day mortality (aOR, 95% CI: 1.166, 1.019-1.333), prolonged hospital stay (aOR, 95% CI: 1.130, 1.051-1.216), more major complications (aOR, 95% CI: 1.147, 1.064-1.235), and decreased overall survival (aHR, 95% CI: 1.058, 1.022-1.095). (Line 305)

FEV1 50-79% predicted: However, there was no significant association between number of medications and 30-day mortality (aOR, 95% CI: 1.027, 0.906-1.164), 90-day mortality (aOR, 95% CI: 1.054, 0.955-1.164), 30-day readmission (AOR, 95% CI: 1.024, 0.949-1.105), or disease-free survival (aHR, 95% CI: 1.010, 0.970-1.051). (Lines 315)

In a subset of patients with FEV1 <50% predicted, the number of prescribed inhaled COPD medications was not associated with 30-day mortality (aOR, 95% CI: 0.988, 0.737-1.324), 90-day mortality (aOR, 95% CI: 0.832, 0.663-1.043),… (Line 319).

Among inhaled COPD medications, only SABAs were associated with increased 90-day mortality (aOR, 95% CI: 1.527, 1.120-2.083) and decreased overall survival (aHR, 95% CI: 1.087, 1.005-1.177). (Lines 331-332).