Peer Review File

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Reviewer A

Thank you for giving me the chance to read and review this interesting and well written paper.
The relationship between co-morbidities and post-operative outcomes is still a matter of debate. The authors used an original method such ad pre-op medications to evaluate that relation. This is an interesting and different point of view of the same old issue.
Because of this, methods should be more clear on how you tried to remove bias such as:
Comment 1: Different kind surgery (lobectomy versus wedge versus pneumonectomy). How the post-op outcomes (morbidity and mortality) in this series are influenced by surgical procedure?

Reply 1: Thank you for this excellent suggestion. As recommended, we have added a supplemental table including rate of major postoperative complications stratified by operation type.

Changes in the text: "Major postoperative complications occurred in 1,351 (13.9%) Veterans and occurred most frequently following lobectomy (n=1,047/5,860, 15.2%). The rate of major postoperative complications stratified by operation type is detailed in Supplemental Table 2." (Added to lines 254-255)

Supplemental Table 2: Rate of major postoperative complications stratified by operation type. (Added to *Supplemental Data*)

Procedure Type	**No Major Complication, n (%)**	**Major Complication Present, n (%)**	
Lobectomy	5,860 (84.84)	1,047 (15.16)	*p<0.001*
Pneumonectomy	116 (1.38)	39 (2.89)	
Segmentectomy	483 (89.44)	57 (4.22)	
Wedge Resection	1,931 (90.28)	208 (9.72)	

Notes: Major postoperative complications were defined as a diagnosis of a pneumonia, empyema, myocardial infarction, respiratory failure, renal failure, or stroke within 30 days after surgery. Interaction between medication count and surgical procedure was not significant in the model.

Comment 2: Another point is nutritional status and anemia. Is it possible to also include this point in your analysis?

English language is good.

Reply 2: A key strength of the present study is that we measured patient comorbidities using the composite Charlson-Deyo Comorbidity Index, which was calculated using ICD-9/10 codes present from 5 years prior to 1 month after surgery. The Charlson-Deyo Comorbidity Index is a validated comorbidity index that is commonly used in clinical outcomes research. As a result, we were able to adjust for the presence of a high number of patient comorbidities in our statistical models. While the Charlson-Deyo Comorbidity Index does not include nutritional status or anemia in its scoring calculation, it does catalog 17 weighted comorbidity conditions that lead to poor nutritional status and anemia such as liver disease or renal disease. However, given the implications of preoperative nutritional status and anemia on postoperative outcomes we do agree with the reviewer that this warrants a comment as a study limitation in the manuscript's "Discussion" section.

Changes in the text: "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 arrythmias, unexpected return to the operating room) in the analysis." (Added to lines 362-366)

Reviewer B

Thank you for the invitation to review. The manuscripts discuss whether prescription medications may be a preferred surrogate parameter for assessing comorbidity and predicting perioperative risk in lung cancer surgery. I have one major comment and a couple minor comments:

Comment 3: Major:

In the introduction and discussion, the authors state that comorbidities are often underreported in hospital administrative data and that prescription medications may be a reliable, easy-to-use, and real-time measure of comorbidity. It would be very informative to present an analysis of whether medication use has a better performance in predicting adverse postoperative events compared to complication use, or even whether a model using both variables has the best model performance.

Reply 3: The reviewer brings an excellent point to light here. The statistical models used in the present study include both medication counts and Charlson-Deyo Comorbidity Index (CCI). Based on the reviewer's comments, we were also interested in testing whether medication use has a better performance in predicting adverse postoperative events compared to comorbidity use. We therefore conducted a supplemental analysis to test statistical model performance with and without CCI. Models were evaluated for information bias using the Akaike information criterion (AIC) statistic and for discrimination using the c-statistic. 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 Supplemental Table 1, this trend was also observed when examining model performance for the outcomes of 90-day postoperative adverse events and overall survival. (Supplemental Table 1). Both parameters suggest better discrimination and model fit with the inclusion of CCI. Given the importance of these findings, we have chosen to clarify this in the "Methods" section of the manuscript.

Changes in the text: "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 Supplemental Table 1, this trend was also observed when examining model

performance for the outcomes of 90-day postoperative adverse events and overall survival. Both parameters suggested better discrimination and model fit with the inclusion of patient comorbidities for the primary and secondary outcomes." (Added to lines 232-241)

Supplemental Table 1. Comparison of statistical model performance with and without Charlson-Deyo Comorbidity Index. (Added to *Supplemental Data*)

Statistical Model	**AIC**	**aOR/aHR in Model for *Total Number of Medications***	**95% CI for *Total Number of Medications***	**aOR/aHR for *CCI***	**95% CI for *CCI***	**C-statistic**
Outcome: 30-day Postoperative Adverse Events						
(+) Medications (-) CCI	7327.489	1.032	1.023, 1.041	N/A	N/A	0.654
(-) Medications (+) CCI	7251.590	N/A	N/A	1.185	1.151, 1.221	0.669
(+) Medications (+) CCI	7241.985	1.016	1.007, 1.026	1.163	1.127, 1.200	0.672
Outcome: 90-day Postoperative Adverse Events						
(+) Medications (-) CCI	7566.017	1.031	1.023, 1.040	N/A	N/A	0.651
(-) Medications (+) CCI	7478.070	N/A	N/A	1.190	1.156, 1.224	0.668
(+) Medications	7469.864	1.015	1.006, 1.024	1.169	1.134, 1.205	0.671

(+) CCI						
Outcome: Overall Survival						
(+) Medications (-) CCI	88536.046	1.027	1.023, 1.031	N/A	N/A	0.6377
(-) Medications (+) CCI	88483.721	N/A	N/A	1.112	1.097, 1.127	0.6398
(+) Medications (+) CCI	88414.940	1.019	1.014, 1.023	1.088	1.072, 1.103	0.6441

Notes: (+) indicates that the listed variable was included in the multivariable analysis, (-) indicates that the listed variable was not included in the multivariable analysis. Abbreviations: aHR: Adjusted hazard ratio; aOR: Adjusted odds ratio; AIC: Akaike information criterion; CCI: Charlson-Deyo Comorbidity Index; CI: Confidence interval; N/A: Not applicable

Minor:

Comment 4: 5 Background: Currently, there is no consensus on how to comprehensively assess comorbidities in lung cancer patients using real-time data.

Disagreement. Comorbidity scores are well established for retrospective outcomes research.

Reply 4: We agree with the reviewer's comments. While comorbidity indices are commonly used in retrospective outcomes research, the published literature and current practice patterns suggest that they are infrequently used in the clinical setting. 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. Alternatively, prescription medications are readily available in most electronic health records and may serve as a more accurate and up-to-date comorbidity measure

for predicting surgical outcomes after lung cancer resection. We will change the text in the abstract to communicate more clearly that comorbidity scores are not commonly used in the clinical care of lung cancer patients.

Changes in the text: "Currently, there is no consensus on how to comprehensively assess comorbidities in lung cancer patients in the clinical setting using real-time data." (Lines 63-64)

Comment 5: 83 While modern electronic health record (EHR) platforms have improved documentation of comorbidities, these data are often incomplete, limiting the applicability of established comorbidity indices, such as the Charlson (CCI) and Elixhauser (ECI) comorbidity indices.

'Furthermore, administrative codes may not reflect disease severity, are infrequently updated, can be discordant between clinicians, and are influenced by hospital billing practices.'

While documentation of comorbidities may be incomplete, isn't the same true for medication documentation?

Reply 5: Thank you for the opportunity to clarify this important point. We believe that prescription medications may be a reliable 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 electronic health record platforms and are reconciled with each clinical encounter, providing a real-time reflection of an individual's current comorbidity status. The Health Information Technology for Economic and Clinical Health Act, enacted under Title XIII of the American Recovery and Reinvestment Act of 2009, identified the creation and maintenance of accurate active medication lists in electronic health records as a national goal. Additionally, administrative data obtained for coding and reimbursement of clinical encounters may not accurately represent a patient's comorbidity burden and has limited ability to determine disease severity or control within a specific diagnosis. 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 patient-specific and can highlight the distinct health factors that may influence an individual's outcomes after treatment for NSCLC.

Changes in the text: None. These points are stated in the "Discussion" section of the manuscript in lines 320-331.

Comment 6: 171 Why is a higher number of prescription medications associated with younger age?

Reply 6: The reviewer has acknowledged an interesting finding from our study. Our findings appear contrary to what has been previously shown in the general population, where polypharmacy has been identified as a growing problem in the elderly population. It is possible that these findings are influenced by the methodology used in our selection of the study cohort. Our study population consists of US Veterans who received definitive surgical treatment for clinical stage I NSCLC. It is well-known that the US Veteran population has higher rates of chronic diseases than the general population, including diabetes, cardiovascular disease, chronic obstructive pulmonary disease, and cancer. Stereotactic body radiotherapy (SBRT) is an alternative treatment modality to surgery to treat clinical stage I NSCLC in patients with multiple medical comorbidities, frailty, and/or poor physical tolerance to undergo an operation. Veterans who are deemed to be poor candidates for surgery can be offered SBRT as an alternative treatment option. Therefore, only medically fit elderly Veterans with low numbers of prescription medications and comorbid diseases are offered surgery. In younger Veterans, there is more heterogeneity in the number of medications prescribed due to a higher rate of selection for surgical treatment.

Changes in the text: None.

Comment 7: Limitations: Isn't sex a very important limitation in your analysis?

Reply 7: We agree with the reviewer's comment that the lack of female representation in our study population is a limitation worth addressing in the "Discussion" section. This lack of gender diversity stems from the fact that the majority of United States Veterans are male.

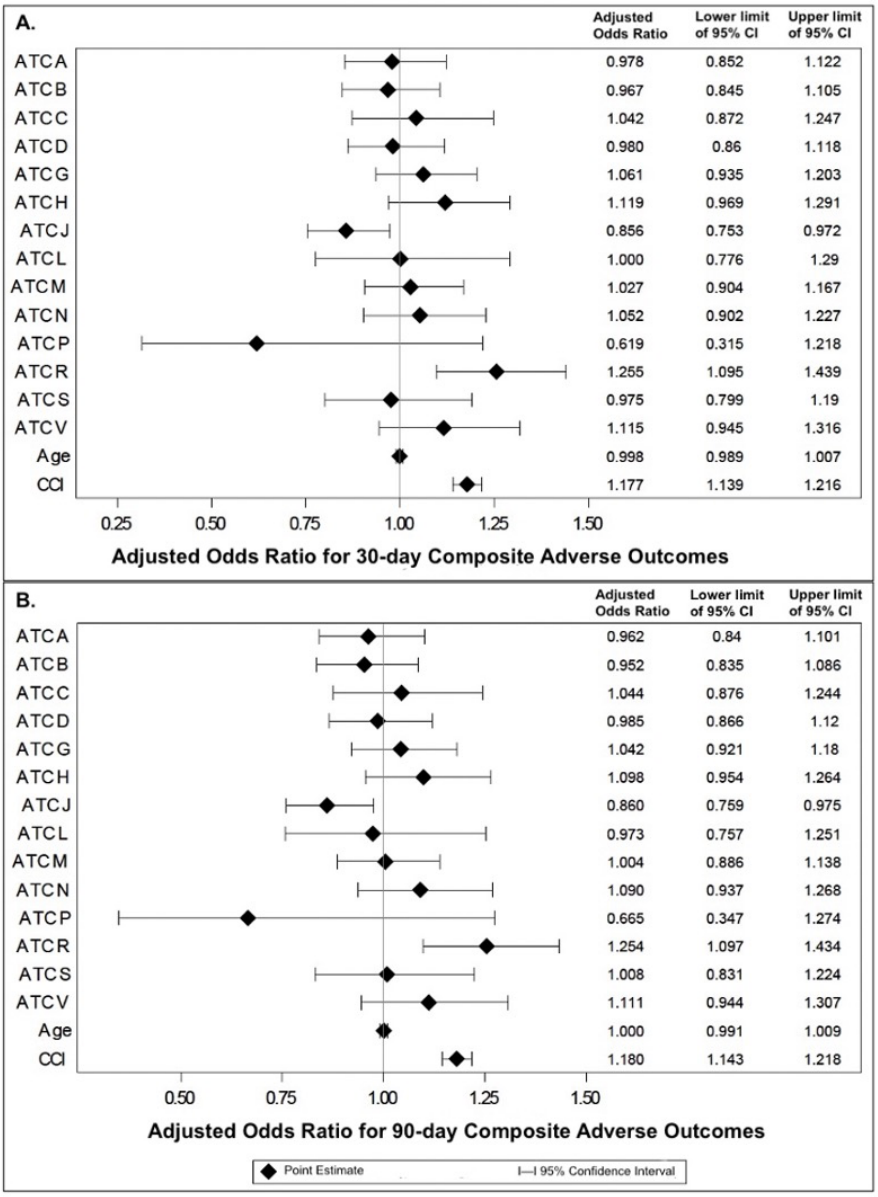
Changes in the text: "As the study population consisted of United States Veterans who were primarily men, additional research is also needed to determine if these findings translate to the population outside of the VHA, including women." (Added to lines 360-362)

Comment 8: I couldn't find an explanation for Figure 3 in the text, Figure A and B are not labeled.

Reply 8: We thank the reviewer for this astute comment. We have erroneously attached the wrong version of Figure 3 with the original submission. It has now been updated to the correct version. We have also appropriately addressed Figure 3A and Figure 3B separately in the manuscript body.

Changes in the text: "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, 95% CI: 1.255, 1.095-1.439; **Figure 3A**) and 90-day (aOR, 95% CI: 1.254, 1.097-1.434; **Figure 3B**) postoperative adverse events compared to patients not prescribed these medications." (Added to lines 279-280)

Figure 3. Association between Anatomical Therapeutic Chemical Level One Class (yes/no) and postoperative adverse outcomes at thirty (A) and ninety days (B) following surgery.



Abbreviations used:
CI: Confidence interval
ATC: Anatomical Therapeutic Chemical class
CCI: Charlson comorbidity index score

Comment 9: How are postoperative outcomes defined?

Reply 9: We thank the reviewer for bringing to our attention that it is not clear how we defined the presence of postoperative complications in the analysis. Postoperative complications were identified using the Veterans Affairs Surgical Quality Improvement Program database, a reliable and validated method for detection of postoperative adverse events, and ICD-9/10 diagnosis codes for complications. We have clarified our methodology in the "Methods" section of the manuscript.

Changes in the text: “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] (Added to lines 223-224)

Reviewer C

An interesting and elegant study adding relevant information on the literature on this topic.

Comment 10: I just have one comment on your design, and I thank the authors for reading and considering it. In lines 143-144 major complications are defined as a diagnosis of a pneumonia, pleural empyema, myocardial infarction, respiratory failure, renal failure, or stroke within 30 days after surgery. I totally agree with the authors that all these must be considered major postoperative complications but the concept of “respiratory failure” could include from PO2<90%, treated with O2 mask, to ICU admission and ventilation. Also, atrial fibrillation, being one of the most frequent, and potentially severe complications after lung resection, is not included. To me, also reoperation due to any complication (bleeding, air leak, etc) should be considered as a major complication.

I’m not suggesting reanalysing the occurrence of complications in your series, since the hypothesis of your study has been clearly demonstrated, but adding a few lines at the discussion section on the limitations of the outcomes definition would be welcome.

Reply 10: We would like to thank the reviewer for their kind review of our work. In this study, postoperative complications were identified using the Veterans Affairs Surgical Quality Improvement Program database, a reliable and validated method for detection of postoperative adverse events, and ICD-9/10 diagnosis codes for complications. Based on the reviewer’s comment, we have clarified this methodology in the “Methods” section of the manuscript. Also, as suggested, we have included the inability to account for all potential postoperative complications as a limitation in the manuscript’s “Discussion” section.

Changes in the text: “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 arrythmias, unexpected return to the operating room) in the analysis." (Added to lines 362-366)