Peer Review File

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Reviewer A

The authors reported that lung cancer patients with underlying COPD have worse symptom burden, using relatively large number of patients. Although current study seems informative to the authors, there are some points needed to be clarified.

Comment 1: It may be difficult to add information such as pulmonary function tests, but smoking history should be added. Because the COPD diagnostic criteria included in the study are vague, smoking history might be helpful in inferring study patient information.

Response: Unfortunately, we do not have access to smoking information and are unable to include or adjust for smoking status or history. We recognize that this is a limitation of our study.

Changes in text: We have added to the limitations section of the discussion (page 14, lines 374 to 376) which reads 'Another limitation of our study was the inability to ascertain smoking status or history and thus we could not address its impact on symptom burden.'

Comment 2. Information on some comorbidities was presented, but if possible, it would be better to present the Chalson comorbidity index, etc.

Response: We used the John Hopkins Associated Diagnostic Groups (ADGs) comorbidity index as opposed to the Charlson comorbidity index (CCI). The CCI was developed to predict mortality risk and thus includes comorbidities (n=19) that are known to increase the risk of death and relies solely on inpatient hospitalization records. We wanted to use a more comprehensive comorbidity index that also measures comorbidity for patients who have never been hospitalized for this study. The Hopkins ADG covers more conditions and clusters them into 32 major ADGs and uses data from both hospital and ambulatory records. This was the rationale for choosing the Hopkins ADG over the CCI.

Changes in text: We have added the mean number of ADGs to table 1 to provide some additional information on comorbidity for the study population.

Comment 3. Although subgroup analysis was performed according to cancer stage, it would be better if detailed analysis according to cancer treatment method is presented (surgery, chemotherapy, and radiation therapy, etc.) .

Response: This is a good suggestion given that patients may experience additional symptoms from treatment, or their symptoms could be alleviated by treatments. However, this goes beyond the scope of our study which was to compare symptom burden around the time of lung

cancer diagnosis. Adding information on treatment would require a significant amount of time, cost and introduce additional complexities such as the timing of treatment in relation to the symptom assessment. For these reasons we are not able to address the impact of treatment on symptoms in our study. We have commented on this limitation in the discussion section (pg 15, lines 387 to 389) which reads 'However, given that time of ESAS completion was not uniform among the population, we cannot comment on whether these differences are affected by lung cancer treatment or persist in the survivorship stage.'

Changes in text: We have not made any changes to the text as we feel this is acknowledged by the above sentence. However, we can elaborate further if requested.

Comment 4. Even though it is difficult to present a relationship with mortality, it would be better that clinical outcome is presented (hospitalization due to respiratory problems, emergency room visits, medical costs, etc.).

Response: This is a great idea however it would require a substantial change to the study methodology (ie. study design, outcomes, analysis, etc). This is well-beyond the scope of our study however we recognize the need for these additional outcomes and we have expanded on this as future research directions in our discussion section.

Changes in text: We have revised the final paragraph of the discussion section (pg 15, lines 390 to 393), which now reads 'We also cannot comment on the impact of symptom burden on the quality of life for lung cancer patients with and without COPD or the impact on healthcare utilization or mortality, which are important directions that should be explored further.'

Reviewer B

I read the paper with great interest in the scope of the important issue of symptoms in lung cancer patients associated with coexisting COPD. The study is well designed, includes a large sample size and is written in a clear and understandable manner.
My suggestions are as follows:

Comment 1. As far as I understand, the data were collected based on the Ontario Cancer Registry, but the criteria for COPD diagnosis in Canada should be discussed. Regarding the GOLD guidelines, FEV1/FVC less than 70% is accepted as obstruction index, but some countries prefer FEV1/FVC less than the lower normal limit to avoid overestimation of COPD in elderly population.

Response: We used a validated case definition for physician-diagnosed COPD (Gershon et al 2009, J Chronic Obstruc Pulm Dis) which includes at least one ambulatory claim or hospitalization for COPD based on ICD-9 codes 491, 492 or 496 and ICD-10 codes J41, J42, J43 or J44. Physicians in Canada should follow the GOLD guidelines for diagnosing COPD, however we know that there are significant barriers to pulmonary function testing (PFT).

Unfortunately, we do not have additional information on how COPD was diagnosed because we do not have access to PFT results to confirm that the FEV1/FVC was <70%.

Changes in text: No changes to the text were made as the case definition which was used for COPD was described in the methods section (page 5/6, lines 139 to 147) which reads 'A previously validated case definition was used to identify individuals with physician-diagnosed COPD using health administrative data. This case definition of at least one ambulatory claim or hospitalization for COPD based on ICD-9 codes 491, 492 or 496 and ICD-10 codes J41, J42, J43 or J44(18) has been shown to have 85% sensitivity and 78% specificity compared to a clinical reference standard(18) and has been used previously to study COPD in Ontario(19,20). Individuals diagnosed with COPD > 90 days prior to lung cancer were considered to have 'previously diagnosed COPD'. Individuals diagnosed with COPD within 90 days prior to, on the day of, or up to 90 days after lung cancer diagnosis, were considered to have 'newly diagnosed COPD'.

However, please let us know if there is additional information that we could provide to clarify how COPD was ascertained.

Comment 2. I think it would be appropriate to emphasize the etiology of diseases that are mostly caused by smoking. I could not find the information about the smoking status of the patients.

Response: Unfortunately, we do not have access to smoking information and are unable to include or adjust for smoking status or history. We recognize that this is a limitation of our study.

Changes in text: We have added to the limitations section of the discussion (page 14, lines 374 to 376) which reads 'Another limitation of our study was the inability to ascertain smoking status or history and thus we could not address its impact on symptom burden.'

Comment 3. In the case of newly diagnosed COPD, there is no certainty that these patients did not already have COPD but were not tested. Unfortunately, it is common for chronic cough to be attributed to smoking or exercise-induced dyspnea and misdiagnosed as a result of aging. Could you please address this concern in the discussion section?

Response: Yes it is most likely that individuals with newly diagnosed COPD were diagnosed with COPD due to the clinical assessment for lung cancer and otherwise their disease may have remained undiagnosed or misdiagnosed.

Changes in text: We have clarified this in the discussion (pg 11/12, lines 288 to 297) which now reads 'It is important to note that patients with 'newly diagnosed COPD' were likely diagnosed with COPD due to the clinical assessment for lung cancer and presumably their COPD may have remained undiagnosed otherwise. It is commonly assumed that 'undiagnosed' COPD is mild and not clinically meaningful. However, our findings show that individuals with 'undiagnosed' COPD (or in our case, 'newly diagnosed' COPD) are symptomatic, which is

consistent with prior studies (12–14).'

Comment 4. Even if cancer stage is included in the analysis, information on treatment is missing. According to current knowledge, the preferred treatment for stage I-IIIA lung cancer is thoracic surgery, often with pre- and/or postoperative chemotherapy. The authors did not discuss the impact of treatment on patient symptoms, although many studies have demonstrated the impact of chemotherapy on PROMs.

Response: This is a good suggestion given that patients may experience additional symptoms from treatment, or their symptoms could be alleviated by treatments. However, this goes beyond the scope of our study which was to compare symptom burden around the time of lung cancer diagnosis. Adding information on treatment would require a significant amount of time, cost and introduce additional complexities such as the timing of treatment in relation to the symptom assessment. For these reasons we are not able to address the impact of treatment on symptoms in our study. We have commented on this limitation in the discussion section (pg 15, lines 387 to 389) which reads 'However, given that time of ESAS completion was not uniform among the population, we cannot comment on whether these differences are affected by lung cancer treatment or persist in the survivorship stage.'

Changes in text : We have not made any changes to the text as we feel this is acknowledged by the above sentence. However, we can elaborate further if requested.

Comment 5. Finally, there is concern about the management of COPD. There is no information on whether patients were receiving appropriate COPD treatment at diagnosis. These circumstances could have an impact on the results by influencing the symptoms reported by the patients.
However, despite these comments, I believe that the paper is valuable and of interest to its readership, and therefore, after addressing the above concerns, should be considered for acceptance by the editorial board.

Response: Thank you for flagging this important consideration. In Ontario health administrative databases, data on medications is only available for those over the age of 65 as only these individuals are covered under the Ontario Health Insurance Plan (OHIP). Among those with previously diagnosed COPD, 71.3% were over the age of 66 (ie. were eligible for medication coverage under OHIP in the year prior to lung cancer diagnosis). We have performed an additional analysis among this subgroup. For individuals with previously diagnosed COPD (aged 66 and over) we looked for records of COPD medications in the one-year prior to lung cancer diagnosis. Individuals were considered to be taking COPD medications if they had a prescription claim for any of the following; long-acting anti-cholinergic (LAAC), long-acting beta agonist (LABA), inhaled corticosteroid (ICS), combination LABA + LAAC, LABA + ICS.

Changes in text: The results from this sensitivity analysis were added to Table 5 & the title of table 5 was revised to read '**Table 5:** Results of the sensitivity analyses: modified Poisson

regression analyses to assess the impact of A. COPD severity, B. COPD management, and C. potential misclassification of COPD on the risk of reporting any moderate to severe symptom.'

We also revised the results section (additional analyses, page 11, lines 267 to 271) which reads 'Among individuals with previously diagnosed COPD, 11,902 were aged 66 and over and had medication data available, of which 60.2% were prescribed COPD medication in the year prior to lung cancer diagnosis. Among this subgroup, individuals prescribed COPD medication had a higher risk of reporting any moderate to severe symptom compared to patients who were not prescribed COPD medication (RR: 1.09, 95% CI: 1.07 to 1.10).'

We added details for this additional analyses to the methods section (additional analyses, page 7 & 8, lines 191 to 197) which reads 'We also assessed the impact of COPD medications on reporting any moderate to severe symptom through a sensitivity analysis of individuals with previously diagnosed COPD who were aged 66 or above. In Ontario, medication data is only available for individuals aged 65 and above and we included a look-back period to capture medications prescribed within one-year of lung cancer diagnosis. Individuals were considered to be taking COPD medications if they had a prescription claim for any of the following classes of medications: long-acting anti-cholinergic (LAAC), long-acting beta agonist (LABA), inhaled corticosteroid (ICS), combination LABA + LAAC, LABA + ICS.'

We also discuss this result in the discussion section (page 12, lines 304 to 307) which reads 'The results of our sensitivity analysis suggest COPD medication heightened the risk of reporting any moderate to severe symptom however this may be a reflection of inappropriate treatment, or simply that individuals with more severe COPD were more likely to be prescribed COPD medication.'

Reviewer C

This is an interesting research topic, used ESAS questionnaire to investigate the impact of underlying COPD on symptom burden among lung cancer patients. COPD increases the risk of lung cancer and multiple studies have identified COPD populations as candidates for lung cancer screening. The clinical association between COPD and lung cancer and possible cancer prevention strategies for this population need to be further explored. In the manuscript, the authors suggested that non-respiratory symptoms (pain, fatigue, etc.) may exacerbate a patient's symptom burden, as well as the impact of undiagnosed chronic obstructive pulmonary disease on patients with lung cancer. However, the authors have not yet offered insights into the degree to which the results of this study suggest and guide prevention and treatment strategies for such patients?

Introduction

Comment 1: In the background the authors give an overview of the studies that are related to symptoms and QoL/wellbeing in patients with COPD and lung cancer They say that

some studies are small, however, there is no clear indication of problems in all previous studies in the literature on the additional burden of disease in COPD versus lung cancer. And there is also no mention of what the additional symptoms are specifically harmful to lung cancer and where the importance of this study lies.
We suggest to write a more structured introduction, as this is difficult to follow:
What is the clinical problem? What has been found thus far? Are there conflicting results? Then The authors can present the aim of the study:
It seems as if their main point is the following: Even though these two diseases commonly co-occur and have a significant overlap in symptoms, little attention has been given as to how the additional disease burden of COPD impacts the severity, number, or type of symptoms that lung cancer patients experience. Given this I would expect to read about the additional disease burden of COPD regarding the severity, number, or type of symptoms. However, that is not very clearly provided. Regarding type of symptom, it's only about shortness of breath (see Figure 2) in patients, independent of stage.

Response: Thank you for these suggestions to improve the clarity of the introduction. We have made changes to improve the clarity and readability of the introduction.

Changes to text: The introduction (page 3/4, lines 64 to 99) now reads 'Chronic obstructive pulmonary disease (COPD) is very common among patients with lung cancer and is associated with poor prognosis(1). Even though these two diseases commonly co-occur and have a significant overlap in symptoms, little attention has been given as to how the additional disease burden of COPD impacts the severity, number, or type of symptoms that lung cancer patients experience. Prior studies among this population have focused on respiratory symptoms, demonstrating that dyspnea is negatively correlated with quality of life and functional status among lung cancer patients(2) and respiratory symptoms are more common among patients with COPD specifically(3,4). However, the generalizability of these studies is limited due to being conducted in single centres, with small sample sizes, and lack of a comprehensive symptom burden assessment which includes non-respiratory symptoms that are common among patients with COPD or lung cancer such as pain, fatigue, and poor mental health (11–13)(5–10). Furthermore, little attention has been given to undiagnosed COPD, which can also be symptomatic(11–13). Undiagnosed COPD is very common among individuals at risk for(14,15) or with lung cancer(16,17). To better guide clinical care it is pertinent to understand the symptom management needs of lung cancer patients with COPD, including those with undiagnosed or newly diagnosed disease. For example, patients with significant symptom burden may benefit from early integration of supportive care and optimization of their COPD-related care.

Understanding the prevalence of symptoms and various combinations thereof, is important to identify the need for symptom management among this population. This can be accomplished through the use of patient-reported outcome measures (PROMs). Cancer centres in Ontario, Canada, routinely assess symptoms via the Edmonton Symptom Assessment Scale (ESAS) which includes nine symptoms(18). Through combining these PROMs with health administrative data, we evaluated symptom burden in a large-scale population-based study. We aimed to determine if underlying COPD—previously diagnosed or newly diagnosed—

increases the collective symptom burden in lung cancer patients, through examining the type, severity, number of symptoms, and total symptom distress scores. We hypothesized that lung cancer patients with COPD have more severe symptom burden compared to lung cancer patients without COPD.'

Methods

Comment 2. Definition of COPD

According to the definition of previous and new COPD, 'previous COPD' diagnosed with COPD > 90 days prior to lung cancer, and 'new COPD' was within 90 days prior to, on the day of, or up to 90 days after lung cancer diagnosis. But is there a possibility that the patient already had some symptoms of COPD in the period you defined of previous COPD, while actually, they were diagnosed lately?

Response: Yes it is entirely possible that they already had some symptoms of COPD but were diagnosed late, or that COPD was found incidentally.

Changes to text: We had revised the discussion to clarify this 'newly diagnosed' COPD, (page 11/12, lines 288 to 297) which now reads 'It is important to note that patients with 'newly diagnosed COPD' were likely diagnosed with COPD due to the clinical assessment for lung cancer and presumably their COPD may have remained undiagnosed otherwise. It is commonly assumed that 'undiagnosed' COPD is mild and not clinically meaningful. However, our findings show that individuals with 'undiagnosed' COPD (or in our case, 'newly diagnosed' COPD) are symptomatic, which is consistent with prior studies (12–14).'

Comment 3. Time interval between the diagnosis of previous COPD and symptoms of ESAS

If there was a big interval between the diagnosis of previous COPD and symptom collection, symptoms still could be affected by previous COPD.

These symptoms, such as anxiety, depression, were produced due to lung cancer, or can be other reasons, like work or life pressure. Whether these symptoms persist, detailed information is needed.

Response: Thank you for these thoughtful suggestions. Symptoms were assessed within 90 days of lung cancer diagnosis. In our results section (page 8, lines 193 to 194) we provide the median time between lung cancer diagnosis and ESAS completion (28 days, IQR: 16 to 48 days). We also provide the time between COPD and lung cancer diagnosis (page 8, lines 195 to 197), which for individuals with previously diagnosed COPD was 9.7 years (IQR: 4.7 to 16.4 years). We cannot comment on whether the symptoms were attributed to lung cancer, COPD, other comorbidities, or as the reviewer has mentioned, life situations.

Changes to text: We have added to the discussion section (pg 15, lines 389-390) 'It is also

difficult to ascertain the cause of the symptoms (ex. lung cancer, COPD, other comorbidities or life situations).'

Comment 4. Stage of lung cancer
You stratified lung cancer with early: I/II and advanced: III/IV. What standard criteria did you base on? Could you please add the references?
Line 175: A standardized mean difference (SMD) > 0.1 was considered statistically significant. What is the reason for his cut-off? Can you provide a reference?

Response: Stage information was gathered from the Ontario Cancer Registry (OCR), which uses a collaborative staging method consistent with the international TNM staging system. Standardized mean difference (SMD) is used instead of p-values because when the sample size is very large, p-values will always be statistically significant. A SMD > 0.1 is a common cut-off for statistical significance in observational studies with a large sample size.

Changes to text: We have added more information on how the stage of lung cancer was ascertained to the methods section (pg 6, lines 161-163), which reads 'Stage of lung cancer was ascertained using the 'Best stage' variable in the OCR, which uses a collaborative method consistent with the tumour, lymph node, metastasis (TNM) international staging system (26)'.

Results

Comment 5. Table 5
You stratified by 'advanced COPD' and 'non-advanced COPD' to address the impact of disease severity on the risk of moderate to severe symptoms. But we only see the outcome table of multivariable analysis and the description of the number of COPD. I think it is better to make a new table or supplementary table of the univariate analyses to describe the variables of 'advanced COPD' and 'non-advanced COPD'.

Response: In table 5, the 'unadjusted' column is the univariate analysis. We have changed the title of table 5 to improve clarity.

Changes to text: The title of table 5 now reads '**Table 5:** Results of the sensitivity analyses: modified Poisson regression analyses to assess the impact of A. COPD severity, B. COPD management, and C. potential misclassification of COPD on the risk of reporting any moderate to severe symptom.'

Discussion
Comment 6. P7-8 295-316 COPD-related symptoms (eg. tiredness and shortness of breath)

These symptoms could also be present in patient with lung cancer and also affected by the stages and severity of lung cancer. Should that be considered and discussed?

Response: This is a great point. These two symptoms (tiredness and shortness of breath) are

not just specific to COPD but are also symptoms of lung cancer as we have indicated in the introduction.

Changes to text: We have revised this sentence in the discussion (pg 11, lines 284-285) to read 'Our findings were largely driven by differences in symptoms with the greatest overlap between lung cancer and COPD (eg. tiredness and shortness of breath).'

Comment 7. P8 320-322, you said "The presence of comorbidities may explain the higher prevalence of non-respiratory symptoms among individuals with previously diagnosed COPD and early-stage lung cancer."

Could you please explain the reason of that and give some references?

Response: This rationale for this sentence is in the preceding sentence, however we understand how this wording is confusing.

Changes to text: We have revised the wording of these sentences in the discussion section (page 12, lines 310 to 314) which now reads 'A higher comorbidity index is associated with reporting moderate to severe symptoms among lung cancer patients(9,10). In our study, individuals with previously diagnosed COPD had a higher comorbidity index and were more likely to have asthma and congestive heart failure compared to individuals with newly diagnosed COPD or individuals without COPD, which may have contributed to their collective symptom burden.'

Comment 8. P8 328-331 Please point out the specific non-respiratory symptoms we should pay attention.

Response: This refers to the symptoms which were more prevalent among individuals with COPD and early-stage lung cancer (drowsiness, lack of appetite, pain, tiredness, and poor wellbeing).

Changes to text: We have revised the text of the discussion (page 13, lines 335 to 338) which now reads 'Regardless of the complex relationship between lung cancer symptoms and comorbidities, our findings suggest that attention should also be given to non-respiratory symptoms, such as drowsiness, lack of appetite, pain, and tiredness when caring for early-stage lung cancer patients with comorbid COPD, as well as consideration of their overall well-being.'

Comment 9. P8-9 332-349 This paragraph clarifies the need for early surveillance for lung cancer with concurrent COPD, compared with previous studies, and what conclusions were drawn from this study, can you get some guidance or suggestions for future surveillance?

Response: The conclusions drawn from this study are stated at the beginning of this paragraph

(ie. need for early and ongoing symptom management of lung cancer patients with coexisting COPD), however we agree that elaboration on guidance for future surveillance would be beneficial.

Changes to text: We have added to the text in the discussion (page 13, lines 353 to 356) which now reads 'In Ontario, efforts should be undertaken to have universal completion of symptom screening by all cancer patients, early in their disease trajectory. Cancer centres or hospitals outside of this province should also consider early implementation of symptom screening to quickly identify and manage patient's needs.'

Comment 10. I do not understand line 301-303, why is this the case?

Response: The reviewer is referring to the sentence 'Our findings also contradict the common assumption that 'undiagnosed' COPD is mild and not clinically meaningful which is consistent with prior studies showing many individuals with 'undiagnosed COPD' are symptomatic.' We understand that the wording is confusing in this sentence and have made changes to clarify the meaning, which is that people often assume that undiagnosed COPD is mild and not clinically meaningful. However we have shown that even lung cancer patients with newly diagnosed COPD (which likely would have remained undiagnosed without the clinical investigation for lung cancer) had worse symptom burden. This means that symptom burden should not be overlooked among individuals with undiagnosed/newly diagnosed COPD.

Changes to text: We have clarified this sentence in the text of the discussion (page 11/12, lines 288-297) which now reads 'It is important to note that patients with 'newly diagnosed COPD' were likely diagnosed with COPD due to the clinical assessment for lung cancer and presumably their COPD may have remained undiagnosed otherwise. It is commonly assumed that 'undiagnosed' COPD is mild and not clinically meaningful. However, our findings show that individuals with 'undiagnosed' COPD (or in our case, 'newly diagnosed' COPD) are symptomatic, which is consistent with prior studies (12–14).'

Comment 11. Lines 317: is this adjusted for age? This also suggests that the COPD/lung cancer patients might be the ones who are heavy smokers.

Response: This is not adjusted for age, however table 1 does also show that individuals with previously diagnosed COPD were older (mean (SD) age: 70.8 years (9.1)) compared to people with newly diagnosed COPD (67.7 years (9.6)) or without COPD (67.4 years (11.0)). Given that we do not have smoking history for the entire study population we do not feel that we can comment on whether this higher comorbidity is related to smoking history.

Changes to text: N/A

Comment 12. A main limitation is that smoking is not included in the analysis, that can be added.

Response: Unfortunately, we do not have access to smoking information and are unable to include or adjust for smoking status or history. We recognize that this is a limitation of our study.

Changes in text: We have added to the limitations section of the discussion (page 14, lines 374 to 376) which reads ‘Another limitation of our study was the inability to ascertain smoking status or history and thus we could not address its impact on symptom burden.’