Reviewer A

Comment: The authors should be congratulated for conducting this large population based analysis of dyspnoea in patients with metastatic NSCLC. They have confirmed that around 70% of this patient population experience this symptom and have highlighted factors associated with the experience of dyspnoea and factors associated with the use of interventions. The authors have highlighted a number of inequities in the receipt of intervention. Their discussion around RT utilisation rates is timely. This manuscript provides valuable "real world" data.
There are a couple of grammatical errors: Line 90 "Focus on to the subset..." and Line 164 "Factors associated with receipt therapy" which should be corrected

Reply: Thank you for alerting us to these errors, they have been corrected.

Reviewer B

Thank you for your interesting and important findings.
You analyzed large number of patients. I think your investigation is very valuable for palliative clinicians to realize that dyspnea is one of the distresses in the end of life.

There are several comments below:

Comment 1: Page 3, line 96: You stated "The details of our data sources and methods have been described previously."
I didn't know how to assess ESAS. I mean it is important to describe how evaluate dyspnea. For example, recall period, or how often did you assess their symptoms using by ESAS. Thus, please described in detail regarding of dyspnea.

Reply 1: ESAS is patient reported, ranked on a Likert scale from 0-10, and typically done at every follow up visit. The administration of ESAS however varies from center to center, and there is no set protocol enforced across the province. Furthermore, each center's protocol in administering ESAS would not be discernable from a large provincial database such as the source database in this study.

We however agree that the use of ESAS can be clarified, and therefore we have modified the line within the introduction (page 3, line 99-101) to say "The Edmonton Symptom Assessment Score (ESAS) is a validated PRO tool used ubiquitously

throughout cancer centers in Ontario, Canada, typically conduced at each outpatient visit"

Comment 2: Page 4, line 120: You described "The primary outcomes of interest were the receipt of interventions at any time from metastatic NSCLC diagnosis to end of follow up." However, these sentences give the impression of an abrupt appearance. There is no mention of these in the introduction. If you are interested in relationship between intervention and dyspnea, it would be better to include the rationale in the introduction as well.

Reply 2: Thank you for this comment. Analyzing the types of intervention for dyspnea and the predictors for intervention receipt are an important goal of this study. We would like to point the reviewer's attention to the last line of the introduction (page 3, line 107-108) where we mention "characteristics associated with the use of interventions commonly used to treat dyspnea in lung cancer."

Comment 3: Table 1: You described "systemic therapy after diagnosis". What was the "systemic therapy". Was corticosteroid included systemic therapy? Please described in detail.

Reply 3: We have added a footnote to Table 1 clarifying that systemic therapy refers to chemotherapy, targeted therapy, or immunotherapy

Reviewer C

Summary of Article
Yan and colleagues submit a manuscript evaluating the prevalence of dyspnea in patients with metastatic non-small cell lung cancer (NSCLC), clinical associations, and treatment patterns. The authors' goals were to determine factors associated with high dyspnea scores, patterns of intervention, and factors associated with receipt of treatment (for dyspnea). To achieve their goals, the authors analyzed administrative data from the Institute for Clinical Evaluative Sciences (ICES) database between 1/2007 and 9/2018. Included patients had available Edmonton Symptom Assessment Scores (ESAS) and were identified in the 2020 Ontario Cancer Registry with metastatic NSCLC (based on ICD-O codes; n=13,159). Exclusions included follow-up <6 months without death or additional cancer diagnoses within 5 years prior to their NSCLC diagnosis. This analysis builds on the authors prior work, which evaluated the prevalence of moderate-to-severe symptoms in patients with metastatic NSCLC. (1)
In this work, the authors stratified patients into groups based on "high dyspnea" (n=9,434) or "low dyspnea," which they defined as any ESAS with a dyspnea score ≥ 4. Comparisons were made between the 2 groups with Student t-testing and Chi-squared testing. Treatments intended to improve dyspnea were included (i.e.,

thoracentesis, pleurodesis, airway stenting, thoracic radiotherapy, and palliative care referral). Multivariable modified Poisson regression modeling was used to predict factors impacting treatment receipt.

The authors found a high prevalence of moderate-to-severe dyspnea (71.7%). Patients with higher dyspnea scores were more likely to: be male, have a higher comorbidity score (Elixhauser Comorbidity Index), live in less ethnically diverse areas, receive systemic therapy after diagnosis, have higher depression and pain scores, and die during the study's follow-up period (noting that patients with high dyspnea scores had a longer time from diagnosis to death). Patients who did not receive dyspnea-directed therapies completed fewer ESAS surveys, were more likely to live in rural areas and neighborhoods with lower income quintiles, and had a shorter time to death from diagnosis. There were also differences in all domains of the Ontario Marginalization Index (deprivation, dependency, instability, and less ethnic diversity). Multivariable regression showed age, sex, comorbidity, rurality, and income quintiles impacted likelihood of receiving some dyspnea-directed treatments.

I agree with the authors regarding the importance of symptoms in lung cancer. As treatments continue to expand (i.e., immune- and targeted therapies) and survival continues to improve, survivorship becomes increasingly important. In addition, clinicians often forget that symptoms, quality of life scores, exercise tolerance, and depression all impact survival in lung cancer.(2-5) More work is needed to identify which patients are at risk for impaired quality of life and design treatment strategies.

Strengths of the article include the large number of patients, sound analysis, and clear writing. I have several suggestions for potential improvement, which I have organized into Major and Minor Recommendations.

Major Recommendations
1. I was confused about several aspects of terminology.
a. In my first reading, I presumed "treatment" was referring to cancer-directed treatments (i.e., systemic therapy, XRT, surgery). Rather, the authors are referring to dyspnea-directed treatments. Clarification earlier in the manuscript would be helpful for the reader.
Reply: Thank you for pointing this out. To provide clarity, we have replaced all instances of the word "treatment" with "intervention", which we have described as dyspnea-associated within the introduction and the methods.

i. Of note, in their prior publication, 47.4% of patients completing ESAS received systemic therapy (the standard of care for metastatic NSCLC). To me, this number is unexpectedly low; could the authors comment on potential etiology and impact to their findings in this submission?
Reply: This is certainly an interesting finding from our prior publications (Tjong et al. 2021). It is possible that many patients with stage IV NSCLC may not be well enough to benefit from systemic therapy. Of note, that cohort included patients up to 2018, which may preclude more widespread adoption of immunotherapy which may be

more likely given to patients who could not tolerate chemotherapy. This reflects the reality of this patient cohort, and we believe emphasizes the importance of symptom-directed therapies like the ones investigated here as many patients are not able to receive/tolerate the standard of systemic therapy.

b. In their prior work, the authors used the term "moderate-to-severe" symptoms. In this submission, they use the term "high" dyspnea score. At first read, I assumed "high" dyspnea score meant severe. Clarifying their definition earlier in the manuscript would be helpful.
Reply: Thank you for pointing this out. We agree that this change in terminology can be confusing. We have changed all instances to be concordant with our previous study, and to use the term "moderate-to-severe".

2. I have a few questions about significant factors associated with dyspnea.
a. I agree with the authors that comorbidity impacts dyspnea, especially COPD. Elixhauser includes "chronic pulmonary disease." Did the authors consider including COPD as a distinct variable?
Reply: We did not include COPD specifically as a distinct variable as it will fall under the umbrella of chronic pulmonary disease. This will include other diseases associated with lung cancer such as interstitial lung diseases.

i. Similarly, I think pulmonary referral is a common intervention for dyspnea. Did the authors consider pulmonary referral in the interventions?
Reply: Thank you for this point. This data was not collected as often these respirologists are involved early on with this patient cohort who have comorbid conditions such as COPD or ILD. We instead chose to look at procedural endpoints such as pleurodesis and thoracentesis, which are often done by respirologists.

b. Building on #1a, systemic therapy can improve symptoms; did the authors consider systemic cancer-directed therapy as a variable?
Reply: This is an excellent point. As we have indicated in table 1, patients with a higher dyspnea score were more likely to receive systemic therapy than those with a lower dyspnea score. We did not specifically describe it as a dyspnea-directed intervention as in table 2, as it is the primary oncologic modality in this patient population, in which the primary aim is often longevity rather than symptom palliation.

c. Is performance status (PS) collected in the database? Lower PS has been associated with worsened survival and higher symptom burden.
Reply: Unfortunately, PS, which we agree is an important variable, is not collected within the database. These data are derived from administrative databases, and therefore clinically assessed variables such as PS are not available.

3. I think the organization of the Discussion could be clearer. Much of the discussion

focuses on etiologies for dyspnea and individual dyspnea-directed treatments (esp XRT and thoracentesis).

a. In my view, the manuscript has 3 main points (and I would make these points discussion highlights):
i. Dyspnea is prevalent in patients with metastatic NSCLC.
ii. Most patients with metastatic NSCLC in the cohort received dyspnea-directed treatments.
iii. Patient factors (age, sex, and comorbidities) and healthcare disparities (rurality, socioeconomic status, and ethnic diversity) impact the likelihood of receiving dyspnea-directed therapies.

b. I think a paragraph dedicated to available interventions for dyspnea would clarify organization for the reader?
Reply: The various dyspnea-directed interventions investigated in this study are laid out within the results section, particularly within Table 2. The discussion is organized and centered around associations between predictors and the receipt of these interventions, which we wish to highlight as the key findings of this study.

c. I would consider a paragraph highlighting the impact of symptoms on survival and survivorship (see references below).
Reply: Thank you for raising this important point and for providing references. We have incorporated some of these studies within the discussion (page 7 lines 258-265), particularly in terms of QoL and depression symptoms as noted in references 2 and 5 that you have provided.

Minor Recommendations
1. The outcome of interest is inconsistently described:
a. Abstract: Outcome of interest = prevalence of a higher dyspnea score.
b. Methods: Outcome of interest = treatment receipt in patients with dyspnea.
Reply: Thanks for highlighting this discrepancy. Both are co-primary endpoints. We have corrected this in the abstract (page 2 line 58-60) and the methods (page 4, line 137-138).

2. I am glad that the authors mention symptom clusters; I would consider adding sleep to the symptom cluster.
Reply: Excellent point, this is added to results with relevant reference (page 6, line 258-259).

3. Lines 151-153: I think there is a redundant clause in this sentence?
Reply: This has been corrected.

4. Line 189: do you mean "a patient's"?
Reply: Correct, thank you.

5. Lines 201-203: "In general, patients who were more marginalized were less likely to receive intervention despite reporting a high score."
a. I think this sentence is SO important and should be a more central component of the Discussion.
Reply: Agreed. This is an area of focus that we expand upon in paragraph 2 and 4 of the discussion. However, aside from marginalized populations, there are other patient characteristics that we would like to highlight, as we have, in the remainder of the discussion.

6. Line 232: This paragraph is narrow. Could it be broadened to highlight the other patient factors: age, sex, and comorbidities?
Reply: This paragraph was to highlight the association specifically with sex and dyspnea, as we did not observe this with age. ECI we have discussed in paragraph 2.

7. Lines 253-255: I would move this sentence to the limitations paragraph.
Reply: Agree, we have moved this to line 341 "Spurious associations may be observed, such as that between dyspnea and sex or race."

8. Lines 265-270, 280-286, and 291-301: these portions of the discussion seem out of place in the manuscript. Much of the manuscript focuses on dyspnea, rather than the details of individual treatments? I think a descriptive paragraph for the procedures would make it clearer for the reader.
Reply: Thank you for this comment. Each of these sections provides a background and then a potential explanation to trends that we observe from this dataset. The first two sections that you have highlighted review the indication for thoracic radiotherapy, its underutilization, and potential reasons for these observations. The last section describes the technical experience requisite of thoracentesis and its association with larger metropolitan centers. We agree that the rationale for perceived risk may be less substantiated and therefore have removed it from the manuscript.

References
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2. Sloan JA, Zhao X, Novotny PJ, et al. Relationship between deficits in overall quality of life and non-small-cell lung cancer survival. J Clin Oncol. May 1 2012;30(13):1498-504. doi:10.1200/JCO.2010.33.4631
3. Hechtner M, Eichler M, Wehler B, et al. Quality of Life in NSCLC Survivors - A Multicenter Cross-Sectional Study. J Thorac Oncol. Mar 2019;14(3):420-435. doi:10.1016/j.jtho.2018.11.019
4. Jones LW, Watson D, Herndon JE, 2nd, et al. Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer. Research Support, N.I.H.,

Extramural. Cancer. Oct 15 2010;116(20):4825-32. doi:10.1002/cncr.25396

5. Sullivan DR, Forsberg CW, Ganzini L, et al. Longitudinal Changes in Depression Symptoms and Survival Among Patients With Lung Cancer: A National Cohort Assessment. J Clin Oncol. Nov 20 2016;34(33):3984-3991. doi:10.1200/JCO.2016.66.8459

Reviewer D

The article is well-written.
Patient-reported outcomes (PROs) are more and more important in clinical practice and in clinical trials.

- Can comment in Methods or Discussion why used the Elixhauser comorbidity index (ECI) - mentioned in line 113 - instead of Charlson´s, for example. Thanks for this question. The ECI was used instead of other indices such as CCI because of several reasons. First, to be consistent with our initial publication (Tjong et al. 2021), we chose to use the same co-morbidity index. Secondly, the ECI was specially developed to be used with large administrative databases using information extracted from ICD codes (Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998 Jan;36(1):8-27. doi: 10.1097/00005650-199801000-00004. PMID: 9431328.). Other comorbidity indices may be more difficult to accurately ascertain without access to individual patient charts.

We have added this latter explanation into the methods (page 4 lines 129-131).

- l. 157: " Patients with high dyspnea scores were more likely to receive intervention with the potential to improve dyspnea, including pleurodesis, thoracentesis, thoracic radiotherapy, and palliative care assessment compared to patients without a high score (p < 0.001 for all)". Can comment subgroups with less palliative care assessment, even though early referral is recommended (as in Temel, NEJM 2010).

- l. 164: well stated that social factors interfere with optimal care, as well as longer survival in those receiving interventions.

- l. 174 - can comment, afterwards, why ageism and sexism may interfere with good care. Fighting against inequities is mandatory. Also l. 256-7.
This is an important point. We have added a line to page 7, lines 242-244 to discuss this point. "Clinicians must be cognizant of internal biases that may compromise the equity of patient care, such as age or sex, so that the principle of medical justice may be upheld."

- Clustering and and PRO instruments are indeed excellent tools to improve symptom management and good-quality palliative care (l. 222-231).
- l. 309: all articles should state their limitations, such as yours. Non-completion of surveys always impacts results. Different treatment strategies due to time eras may show different results, in comparison with modern strategies.
- The Conclusions: "This population-based analysis demonstrates that nearly three quarters of patients with metastatic

331 NSCLC in Ontario report significant dyspnea. Most patients with high dyspnea scores receive

332 intervention although disparities exist based on patient and social factors. These data of symptom

333 burden and patterns of care can help inform policymaking and guide the astute clinician in identifying

334 patient populations at risk of suboptimal care." Very good article finalization and summary.