

## Peer Review File

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### Reviewer Comments

Thank you for the opportunity to review. This topic is significant and can add to the literature. However, several notable major concerns need to be addressed.

Major concerns:

Background and rationale:

**Comment 1:** Authors need to do a better job describing what the gap is. Plenty of studies have (with larger Ns) have examined quality of life and symptoms in lung cancer. Dave Cella's group has conducted rigorous research in which they obtained clinician and patient feedback on which symptoms and quality of life concerns are most important to address (that is how they developed their PROs). I do think this study adds, but the gap that's currently articulated is vague and not well-aligned with what you actually did ("small, narrowly focused-sample size, lack of patient-centric methodology" – this isn't really true).

**Reply 1:** We agree that many studies, including those by our colleague Dr. Cella, have examined the quality of life and symptom burden. However, unlike many of the PROMIS initiatives, this study was focused specifically on a well-defined group with documented lung cancer. This disease-specific approach has certain advantages to studies that involve only members of the general public. Specifically, patients with lung cancer have a unique profile of symptomatic burden. We aimed to study this burden specifically with our study. Our study adds to current knowledge regarding disease burden in lung cancer. Specifically, it evaluates patient-reported disease burden in lung cancer using a well-defined, relatively large, cohort of patients recruited from a tertiary medical center and from the Go2 Foundation for Lung Cancer.

We edited the wording in the highlights box and in the introduction's background section to better encompass what prior studies have looked at and to show how our study adds to knowledge of patient-reported disease burden in lung cancer. We also added references to Dr. Cella's work in lung cancer and developing a functional assessment for cancer therapy.

**Changes in the text 1:** The second bullet point of the highlights box has been changed to the following: "As survival rates in LC increase, there is a need to better understand what issues and symptoms generate the highest degree of disease burden in LC and develop ways to lessen this burden over time." See page 5.

The following has been added to the background section of the introduction: "Research has also been done to elicit the symptoms that cancer patients find important and to develop and validate patient-reported outcome measures, like the Functional Assessment of Cancer Therapy (FACT-G) scale and the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale, which may be used

in oncology clinical trials. (8,9) Although previous research has greatly contributed to the understanding of symptom impact on the lives of those with LC and has even led to the generation of useful outcome measures, a clearer understanding of how a patient's disease burden is affected by the many issues and symptoms that occur in LC is needed." See page 5, lines 124-131.

The following has been added to the rationale and knowledge gap of the introduction: "Research that focusses on well-defined groups of patients across multiple stages and types of LC are also of value. Such research is especially useful when future studies look to define particular clinical trial inclusion criteria, study LC disease progression longitudinally, and evaluate how individual or combinations of treatments affect distinct patient groups." See page 6, lines 136-140.

Methods:

Qualitative interviews –

**Comment 2:** Need to add description of how patients were sampled and rationale. For example, it does not appear that purposive sampling was done to ensure representation in interviews with respect to sociodemographic or clinical features. Rather, it seems like this was just a convenience sample. This is a major limitation because your survey was informed by the results of your qualitative interviews. If you didn't have good representation in the qualitative interviews, your survey may have missed some important concerns.

**Reply 2:** Potential interview participants were referred by partnering oncologists at a tertiary medical center. Physicians were specifically requested to refer a broad and diverse sample (in terms of demographic, clinical, and treatment features). We acknowledge that there are some limitations regarding this approach. Of note, these interviews were utilized as an exploratory mechanism. To this end, during our cross-sectional study of 139 patients, we provided a free text portion of the survey where patients could identify any symptom not mentioned. In this way, patient input was not restricted to the data obtained from the original interviews. We highlight this in the text.

**Changes in the text 2:** We added the following text to the limitations section of the discussion: "In particular, potential interview participants were referred by partnering oncologists at one tertiary medical center. Physicians were specifically requested to refer a broad and diverse sample (in terms of demographic, clinical, and treatment features); however, all interviewees received care at the same center. In contrast, participants in our cross-sectional validation study represented a more geographically diverse population." See page 10, lines 344-348.

**Comment 3:** Recommend adding your interview guide as supplemental material. The Results section states "When a participant was asked, "What type of functional limitations are most important to a patient with lung cancer?" – is that an actual question posed? That's a very high literacy question.

**Reply 3:** The qualitative interview guide has been included as a supplemental attachment. Yes, the question “what type of functional limitations are most important to a patient with lung cancer?” was asked to participants. We inquired if participants understood the questions. As needed, individual questions were reworded or further explained during the interview process.

**Changes in the text 3:** We added the following statement to the methods section of the text: Interview guides “are included as a supplemental attachment.” See page 7, line 180.

**Comment 4:** Recommend providing coding scheme used (e.g., how were coders to distinguish between social role dissatisfaction vs. social role limitations)

**Reply 4:** Coding of direct quotes from the interviews into symptoms and symptomatic themes was conducted independently by two members of the research team. Qualitative framework methodology and an investigator consensus approach were subsequently used. In the specific case of social role dissatisfaction vs. social role limitations, the prior included symptoms that were stated to cause more emotional stress to participants, such as inability to do things previously done, social isolation, impaired interaction with family members, and exhaustion from social interactions. The latter included symptoms that caused more physical limitations to participants or caused participants to need to restructure their activities, such as decreased independence, reliance on family members, reliance on others, and the need for increased planning prior to social interactions.

**Changes in the text 4:** No changes were made in the text in response to this comment. Please refer to the study design in the methods section (page 7) for a description of the coding process.

Quantitative-

**Comment 5:** Could people identify more than one treatment modality for lung cancer? Combination chemo-immunotherapy is fairly common. Are these patients reflected in both the chemo and the immuno sub-analyses?

**Reply 5:** Yes, participants were able to identify more than one treatment modality for lung cancer. During the cross-sectional study, reception of immunotherapy, chemotherapy, and targeted therapy were asked as three separate questions in the demographics form. In subgroup analyses using cross-sectional study data, three separate analyses were done for participants who received immunotherapy, chemotherapy, and targeted therapy. For example, a participant who received combination chemo-immunotherapy, would be grouped into the treatment group during the immunotherapy analysis, grouped into the treatment group during the chemotherapy analysis, and grouped into the non-treatment group during the targeted therapy analysis.

**Changes in the text 5:** No changes were made in the text in response to this comment.

Analysis:

**Comment 6:** Age (above vs. below mean) was statistically driven rather than conceptually driven. Seems the literature has plenty of examples of older age (e.g., 70+) being associated with different concerns than those younger. Might want to consider a conceptually-based age cutoff rather than sample-specific mean.

**Reply 6:** We acknowledge that a conceptually-based age cutoff has some value in a lung cancer subgroup analysis. However, we predetermined our statistical analysis prior to conducting this research, and our criteria required this specific approach.

**Changes in the text 6:** No changes were made in the text in response to this comment.

Results:

Qualitative –

**Comment 7:** Describe the sample who participated in the qualitative interviews and how they differed/did not from the sample approached. The refusal rate was high – need to provide reasons people declined.

**Reply 7:** Unfortunately, we did not collect demographic information or specific reasons for refusal from participants who declined to take part in the qualitative interviews. Of the 14 individuals who were contacted and declined to participate in the interviews, 12 were lost during communication/follow-up, 1 was not interested, and 1 was unavailable due to poor health.

**Changes in the text 7:** We added the following statements to the results section on phase 1 LC qualitative interviews: “Out of a total of 29 adults with LC from University of Rochester clinics who were provided information about this study, 15 individuals participated in interviews. Of the individuals who elected not to be interviewed, 12 did not respond to a follow-up communication, one later stated that they were not interested, and one was not available due to poor health.” See page 8, lines 241-244.

Quantitative –

**Comment 8:** Need to provide information about how many people we contacted through the registry – not just the number who opened the survey (if these data are available). Otherwise, the response rate is very hard to determine.

**Reply 8:** We partnered with the Go2 Lung Cancer Foundation, Lung Cancer Registry to recruit participants for our cross-sectional study. The Registry performed outreach via email to its members. We do not have information on exactly how many emails were sent out or opened. However, we do have information that, as of January 2021, when the cross-sectional study was conducted, there were 2256 participants. Of the Registry members who were contacted, 160 people opened the survey and 139 responses were included in data analysis as per our pre-specified protocol.

**Changes in the text 8:** We added the following to the methods section: “Potential participants had no prior contact with the study team; these individuals responded to emails sent out by the GO2 Foundation’s Lung Cancer Registry, which comprised 2256 members as of January 2021.” See page 7, lines 197-199.

**Comment 9:** Was “difficulty running” a symptom identified by the qualitative portion? It’s a very specific and somewhat unexpected concern to arise, almost indicative of a sample that likely had much higher physical function than many patients with lung cancer (vs. inability to do things previously done is a really common one we see in this population).

**Reply 9:** Yes, “difficulty running” was identified by one participant twice during our qualitative interviews. During the cross-sectional study, this symptom showed a prevalence of 76.3%, an average life impact of 2.04, and a population impact of 1.56, which suggests that it was quite important to the individuals with lung cancer we sampled. This provides an example of the identification of an important issue to patients with lung cancer which is not generally or widely known.

“Inability to do things previously done” was also a common symptom. During the cross-sectional study, this symptom showed a prevalence of 78.5%, an average life impact of 1.76, and a population impact of 1.38, which suggests that it was about as prevalent as “difficulty running” but less impactful on participants’ daily lives.

We would hesitate to say that our sample was significantly healthier/of higher physical function than the average population with lung cancer: nearly 80% of participants in the cross-sectional study reported stage III or IV lung cancer, and more than 70% were receiving treatment. We do recognize that there is likely a degree of error or misrepresentation in this patient-reported data and that participants with very high disease burden may not have been capable of participating in this research (as we stated in the strengths and limitations section of the discussion).

**Changes in the text 9:** No changes were made in the text in response to this comment.

Limitations-

**Comment 10:** Recommend changing language around “not perfectly representing” to clearly state that your sample is not representative of lung cancer patients in x, y, and z ways (sex, educational attainment, to some degree age – average age for lung cancer patients is older than your sample’s M), smoking history)

**Reply 10:** We modified the language around the limitations and representativeness of the sample cohorts in our study as requested.

**Changes in the text 10:** We changed/added the following statements in the discussion strengths and limitations section: “While these demographic features are not atypical of registry studies,

they likely do not represent the demographic profile of all individuals affected with LC, specifically in terms of sex, race, ethnicity, and educational attainment.” See page 10, lines 350-353. “Participants in our research may also not have accurately represented the broader lung cancer population in terms of smoking history.” See page 11, lines 355-356.

**Comment 11:** Recommend noting that you did not include psychometrically validated measures of self-reported physical/mental health or quality of life. Those measures could have functioned as “known groups” (e.g., patients with poor physical health reporting more x, y, z concerns).

**Reply 11:** We added a statement pointing out that future research should consider exploring if there are additional differences in symptom profile based on the scores of psychometrically validated patient-reported measures of physical and mental health.

**Changes in the text 11:** We added the following statement to the discussion implications and actions needed section: “Future studies should consider exploring if there are additional differences in patient symptomatic profiles provide based on clinical state and the scores of psychometrically validated patient-reported measures of physical and mental health.” See page 12, lines 436-439.

**Comment 12:** Need to note small sample size regarding qualitative interviews, lack of sampling strategies to ensure representativeness for qualitative interviews.

**Reply 12:** We conducted qualitative interviews according to previously proven qualitative research techniques and until data saturation was reached (see reference below).

Reference: Green J, Thorogood N. *Qualitative methods for health research*. 4th ed. London: Sage; 2004.

A sample size of n=15 for the semi-structured qualitative interviews is derived according to the principles of phenomenological qualitative research using criterion sampling, in which participants meet predefined criteria. Interviews are conducted until data saturation is reached and no new analytical information arises, providing maximum information on the phenomenon. Data saturation is generally reached with a sample size of 15 in phenomenological qualitative research; however, a review of the analysis, findings, and the quality of the participant quotes collected determines whether sampling may conclude due to data saturation. In some situations, two or three more interviews may be conducted to confirm that data saturation has been reached. In this case, 15 interviews were sufficient to elicit the symptoms and themes of importance in our sample cohort. In the paper we acknowledge the recruitment methods and limitations of our sample and the use of one recruitment source for the qualitative interviews.

**Changes in the text 12:** Refer to Changes in the text 2. We added the above reference to *Qualitative methods for health research* to the methods section where interviews and data saturation are mentioned. See page 7, line 194.

Comparison with similar research:

**Comment 13:** Move discussion of smoking representativeness to Limitations.

**Reply 13:** The discussion of smoking representativeness was moved as requested.

**Changes in the text 13:** The discussion of smoking representativeness was moved to the limitations section of the discussion. See page 11, lines 355-364.

**Comment 14:** This section needs to talk about how the symptoms and concerns identified in your study sample converge or diverge from prior literature. To me, it seems like the emphasis on social/role dissatisfaction and limitations is something that stands out. We typically focus on lung cancer symptoms and tx toxicities like fatigue and overlook functional concerns. The concern about sexual function also seemed like one that is overlooked. To really add to the literature, you need to say how what you found is advancing what we know and how we should change/not change assessments in clinical practice.

**Reply 14:** A few paragraphs were added to compare our study's findings to those of prior studies, especially in terms of physical, emotional, and social symptoms that are prevalent and impactful in those with lung cancer. A paragraph was also added to discuss the importance of functional limitations on lung cancer patients' quality of life and how our research adds to the literature in this area.

**Changes in the text 14:** The following text was added to the comparison with similar researches section of the discussion:

“Many of the findings from our research were consistent with those reported in prior studies. For example, we found fatigue, impaired sleep and daytime sleepiness, and limitations with physical function to be among the most prevalent symptomatic themes in our study cohort, and inability to do activities and fatigue to be among the most impactful symptomatic themes. Using the Lung Cancer Symptom Scale, Iyer et al showed that persistent cough, fatigue, and shortness of breath were the most prevalent symptoms in a U.S. sample of LC patients; Iyer et al also showed that fatigue, loss of appetite, respiratory problems, cough, pain, and blood in sputum were the most frequent symptoms and that loss of appetite, fatigue, pain, and shortness of breath were most impactful in a sample of LC patients from France and Germany. Similarly, Gift et al demonstrated that fatigue, nausea, weakness, loss of appetite, weight loss, and vomiting were the most frequent patient-reported symptoms that impaired daily functioning in patients who were recently diagnosed with lung cancer, across 24 hospitals and clinics. Montazeri et al presented findings that were congruent to those by Iyer et al and Gift et al in a population-based study with 129 patients in Scotland.

In our study, emotional issues was also a highly prevalent symptomatic theme, and social role dissatisfaction was highly impactful. Prior studies largely focus on the physical burden and toxicities of LC, but a few studies like those by Tishelman et al and by Ostlund et al demonstrate that self-perception and emotional functioning play a significant role in lung cancer patients' QoL. Interestingly, individuals with lung cancer in our interviews and cross-sectional study placed an emphasis on functional limitations, like difficulty running, impaired sexual function, and inability to do things previously done as greatly affecting their lives. Indeed, in a study by Leppert, more than 90% of patients with advanced lung cancer complained of limitations in performing occupational roles or pursuing hobbies. Such symptoms that decrease daily function are often under-recognized by physicians who treat LC patients and by researchers searching for symptomatic targets and treatments for these individuals. Our research suggests that increased attention on and addressing the functional effects of lung cancer may help alleviate LC burden.”

See page 11, lines 372-396.

**Comment 15:** My apologies for the delayed review! Overall, this manuscript can add to the literature, but there are some methodological limitations that need to be acknowledged and authors need to do a better job of placing their findings in the context of the broader literature.

**Reply 15:** Thank you very much for your thoughtful review! We have incorporated your edits and suggestions to the best of our ability. We believe these improvements have added to the context of our research and the clarity of the manuscript.