Reviewer’s report

Title: The association of depressive symptoms, personality traits, and sociodemographic factors with Health-Related Quality of Life and Quality of Life in patients with advanced-stage lung cancer: an observational multi-center cohort study

Version: 0 Date: 13 Nov 2019

Reviewer: Lisa M. Gudenkauf

Reviewer's report:

Major Issue:
1. Contribution to the literature - The authors describe this study's unique contribution to the literature as the examination of personality factors and general quality of life (including environment and spirituality), yet the title, abstract, and results/discussion focus on the relationship between depression, performance status, and health-related quality of life (HRQOL). The authors indicate in the introduction that the associations between HRQOL, performance status, and depression have previously been established in the literature, so it is not clear how results of this study add to this knowledge. It is also not evident from the title that personality traits are a focus of this study. If significant results with general QOL and personality factors are limited, these still need to be discussed. It would be helpful to specify the non-significant results and further articulate how the results of the present study add to the existing literature.

Minor Issue:
2. Some phrases throughout the manuscript are vague, somewhat difficult to understand or follow, or grammatically incorrect (examples below). There are also some typos ("should be prevented.""); Introduction, third paragraph) and font differences (Intro, 2nd sentence):
   a. "…treatment is in most patients with advanced disease lung cancer associated with…” (Intro, 1st paragraph, 3rd sentence)
   b. "Contemplating on these considerations, we aimed to … established their importance among known variables" (Intro, 4th paragraph, 1st sentence)
   c. "We analyzed to which extent…” (Intro, 4th paragraph, last sentence)
   d. "Openness reflects to an open attitude…” (Methods, Study Measures, NEO-FFI paragraph)
   e. "Figure 1 demonstrates the selection of patient." (Results, Patient Characteristics, 1st sentence)
   f. …EORTC QLQ-C30 scales according tot the simple linear regression analyses…” (Methods, Statistics, 5th sentence)
   g. "Considering that HRQoL reflects merely to those components of QoL…” (Discussion, 1st paragraph)
   h. "We hypothesized whether the absent effect…” (Discussion, 2nd paragraph)

Further section-specific comments are listed below:

Abstract
1. Rationale for the present study provided in the opening sentence is vague. It is unclear why the selected sociodemographic, personality, depression, and QOL factors were examined based on this rationale. For example, how would examination of personality factors offer opportunities to enhance patient care during chemotherapy? Generally speaking, the rationale should speak to constructs or factors being examined, rather than "variables" that will be statistically analyzed.
2. Rather than generally listing the measures used, it would be helpful for the reader to see the measures categorized by the constructs being measured (e.g., personality, depressive symptoms, and QOL).

3. It is not clear in the abstract why a $p \leq 0.10$ is used, and the abstract does not specify what level of multiple linear regression results are considered significant (e.g., $p \leq 0.05$).

4. Results of analyses involving personality measures are not reported.

Introduction

1. The importance of considering QOL in the context of cancer treatment goals has been well-established for some time. What do the authors mean by "earlier" in the second paragraph?

2. The distinction between HRQOL and QOL is not clearly articulated in the introduction or throughout the manuscript. If there is additive value to including a general QOL measure and these are being treated as distinct constructs, collapsing them as "(HR)QOL" in the title and abstract creates confusion for the reader. Further, the specific value of assessing "additional concepts, such as the environment and spirituality" could be elaborated upon with literature underscoring the previously established importance of these concepts in relation to depressive symptoms and how they impact "a patient's well-being."

3. The third paragraph of the introduction is difficult to follow, and the rationale for examining personality factors is not clearly articulated. A potential reason for examining personality factors is described as "identifying patients who are prone to low levels of (HR)QOL at the start of treatment." Would there be added benefit to assessing personality traits in addition to directly measuring (HR)QOL at the start of treatment? In the introduction, the authors suggest identification of key variables related to (HR)QOL for the purpose of targeting supportive care interventions. How would the authors suggest translating the measurement of personality traits into clinical practice? Would personality traits be used as selection criteria for a supportive care intervention? The malleability of trait vs. state factors is also not addressed. To what degree are the measured personality factors truly changeable with supportive care interventions?

4. Based on the final sentence of the Introduction, the reader is led to believe that the key factors being examined in the present study are (HR)QOL, depressive symptoms, and personality, but this list is not consistent with what is suggested by the title or other sections of the manuscript.

Method

Study Population

1. Did the authors unresectable mesothelioma patients in the present analyses? If so, it would be helpful to speak to precedents for grouping mesothelioma as part of a lung cancer cohort and the potential similarities and differences of NSCLC and mesothelioma patients, and it could be useful to statistically check for any potential differences.

2. The Study Population section indicates that patients had "started treatment," causing the reader to question when in treatment each patient completed study measures. This is a very important question when considering patient's (HR)QOL. The authors do answer this question but not until later, in the final paragraph of the Study Measures section (first day of the first cycle). Perhaps this paragraph
would be more helpful after the Study Population section as an explanation of the overall process for measure administration. Additionally, if patients received different treatment protocols (pemetrexed in combination with cisplatin or carboplatin as either first list or with pemetrexed monotherapy as second line), treatment type should be considered as a covariate.

3. What were the physical or mental conditions that prevented patients from completing the questionnaires? Could another individual help them complete the questionnaires with the patient articulating their own answers? How does this exclusion criteria map on to Figure 1? The Methods section says that patients were excluded if they could not complete the questionnaires, but Figure 1 shows that 0 patients were excluded. What were reasons for non-completion of questionnaires (N=26)?

Study Measures
4. For each of the measures, provision of example items could be helpful so that the reader has a better understanding of exactly what is being assessed (e.g., WHOQOL-BREF domains: Physical Health, Psychological Health, Social Relationships, and Environment).

5. In the WHOQOL-BREF paragraph, "Worst response" and "Best response" appears as a subjective judgment of responses. Does this refer to "worst quality of life" and "best quality of life?"

6. The authors generally report "satisfactory psychometric properties" for the WHOQOL-BREF but "relatively low Cronbach's alpha" for the Social Relationships domain. Similar general descriptions are provided for all measures. Specific values are not reported, and it is unclear what metric is being used to determine "satisfactory," "acceptable," and "good" psychometric properties. Additionally, psychometric properties are only provided with respect to the broader literature, and no sample-specific values are provided.

7. In the EORTC-QLQ-C30 paragraph, please list the specific number of items assessing symptoms or problems rather than stating "several."

8. In the STAI paragraph, what was the rationale for specifically selecting the 10-item STAI trait anxiety subscale?

9. The CES-D selected to measure depression contains a somatic domain that has been argued to overlap with physical symptoms of cancer and cancer treatment. Could the authors speak to their rationale for selecting this measure and how this potential issue was addressed?

10. In the NEO-FFI paragraph, the sentence grouping of neuroticism with extraversion and openness with agreeable creates confusion for the reader, suggesting a specific contrast of those construct pairs. Additionally, definitions for agreeableness ("relates to orientation in other people's experiences, goals, and interests") and conscientiousness ("refers to the conscience as a guiding and reflective instrument") are not entirely understandable. Perhaps reframing definitions with reference to the degree to which an individual demonstrates particular characteristics would be helpful.

Statistics
11. What is the "m" (number of predictors) for this study? How were the specific sociodemographic and clinical variables selected? It appears from the list of variables in the Methods section, that smoking status, history, cancer stage, and disease response were omitted from analyses. Why were these measured and not analyzed? The authors specifically identify age and gender as a priori,
empirically-based covariates in this section, but in the introduction section, education and marital status are also listed as having been associated with HRQOL in the literature. Why did the authors select age and gender selected but not education and marital status?

12. It would be helpful to keep the list of sociodemographic variables consistent across the manuscript:
   a) Methods: Age, gender, educational level, ethnicity, employment, marital status, smoking status
   b) Results: Age, gender, ethnicity, education, employment, partner status

13. Similarly, it would be helpful to keep the list of "clinical information" consistent:
   a) Methods: History, cancer stage, disease response, ECOG performance status
   b) Table 1: Cancer stage, type of tumor, line of therapy, ECOG performance status

Results
1. Table 2: The IQR is provided, but adding the full possible range of scores might also be helpful to put the mean and median into context in terms of potential clinical meaningfulness.

Linear Regression Analyses
2. What is the reference point for the statement "...the association with the CES-D score was the strongest"? To what other associations is this being compared?

3. Tables 3 and 4: How were the specific orders for variables in each backwards stepwise regression determined? What explains the differential selection of variables for the different subscales?

Discussion
1. The discussion section identifies this study as being the first prospective multi-centre observational study to report the association of personality and depressive symptoms with (HR)QOL in patients with advanced-stage lung cancer. However, NEO-FFI personality traits were not associated with (HR)QOL, except for conscientiousness (specifically with the Physical Health domain of the WHOQOL-BREF). Similarly, trait anxiety was associated with only two (HR)QOL scales/domains, namely Role Functioning (EORTC QLQ-C30) and Environment (WHOQOL-BREF). After removing depressive symptoms from the model, the authors conclude that "the results emphasize the importance of trait anxiety, especially in the absence of depressive symptoms." This statement could be further clarified to explain this importance and specific subscale findings. The paragraph concludes with the statement, "Therefore, the effect of personality (i.e., except for trait anxiety) on (HR)QoL may be less important in patients with lung cancer." This is a comparative statement, and it is unclear to which other population lung cancer patients are being compared. Why might this be and what are the clinical implications? Furthermore, the differing conclusions drawn regarding personality factors and their importance in this study (as well as the differing level of emphasis in different sections of the manuscript) creates some confusion for the reader.

2. Explanation of specific study findings would strengthen the discussion section. What do the authors make of the following specific findings?
   a) CES-D score was negatively associated with the General Facet and with all WHOQOL-BREF domains, except Social Relationships
   b) For both WHOQOL-BREF and EORTC QLQ-C30 domains/scales, except for Environment, the association with CES-D was the strongest

3. The third paragraph discussing unexpected results would be strengthened by offering more
thorough interpretation and possible explanations for the findings and relationships among constructs in layman's terms and in clinically relevant language rather than speaking strictly to statistical methods. For example, rather than stating "the alternative explanation, i.e., the positive direction of the beta is a true observation, seems rather unlikely," it would be helpful to explain why the result is unlikely based on what the literature shows about the relationships between the constructs of interest.

4. Further elaboration on study strengths could help highlight the contributions of this study to the broader literature.

Conclusion

1. The sentence, "Our results demonstrated that physicians are recommended to have high awareness for patients with depressive symptoms and those with ECOG performance status of 2 or higher at the start of treatment as they may have low levels of (HR)QoL" could benefit from revision.
   a) How do results demonstrate that physicians are recommended?
   b) How do the authors propose that physician awareness be increased? What measures would be recommended to assess depressive symptoms in the clinical setting? How would assessing depressive symptoms in order to predict (HR)QoL be advantageous over directly assessing (HR)QoL using an available measure?
   c) This is the first time that an ECOG performance status of 2 or higher is specifically targeted as a cut-off. Can the authors speak more to this?
   d) Perhaps the authors could speak more to what the literature shows with regard to the long-term consequences of depression and low (HR)QoL at the start of treatment and what could happen without intervention as a means of strengthening their conclusions.

2. What specific interventions would the authors recommend as being designed to prevent a deterioration of (HR)QoL? What does the literature suggest?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
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No

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