Author’s response to reviews

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

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Author’s response to reviews:

Response to the reviewers’ comments

Manuscript title: Depressive symptoms and performance status are associated with (Health-Related) Quality of Life in patients with advanced-stage lung cancer: an observational multi-center cohort study (BCAN-D-19-01412)

We thank the reviewers for the valuable comments that helped to improve the content of the manuscript. We have taken notice of the reviewers’ comments and have revised our manuscript in accordance with the given suggestions.

Editorial Staff:

1. Please rename 'Introduction' to 'Background'

Response: We thank the editor for pointing this out.

Changes to the manuscript:
Introduction was renamed to Background.

2. Please move tables to after the references
Response: We thank the editor for pointing this out.

Changes to the manuscript:
Tables are moved to after the references.

Lara N Traeger (Reviewer 1):

Main points

I recommend clarifying the authors' differentiation between HRQOL and QOL. The manuscript description, that "HRQOL measures only patients' feelings related to their health, while QOL also reflects additional concepts such as the environment and spirituality," suggests that HRQOL may be subsumed within QOL. It would be helpful to distinguish the two constructs, along with careful attention to measurement differences between general versus health-related versus disease-specific measures of quality of life and the purposes of each in research or clinical contexts.

Response: We thank the reviewer for this comment.

Changes to the manuscript: A new section was added to the introduction that further discusses these differences:

HRQoL focusses on health and represents the impact of disease and treatment on the feelings patients have about their functional capabilities and well-being (1). QoL assesses patients’ feelings (i.e., satisfied or bothered) about their functioning and well-being in at least three key areas (i.e., physical, psychological and social well-being). It also evaluates a patient’s feelings related to their environment (e.g., satisfaction with living conditions) or spirituality (e.g., meaningfulness of personal life). A recent study underscores the additional value of spirituality for a patient’s well-being as it observed that better cognitive and emotional functioning was seen in cancer patients with higher spiritual well-being (2). Patients with better global Health Status/QoL also had higher spiritual well-being. In addition, besides the additional assessment of a patient’s environment and spirituality, a QoL instrument also contains positively phrased items.

In studies that investigate new therapies in lung cancer, often HRQoL is evaluated and not QoL. These studies evaluate HRQoL to determine the impact of treatment on cancer patients well-being. QoL may be used in a similar manner and provides further information as it enables a more comprehensive assessment of a patient’s well-being than HRQoL. In a clinical setting, application of HRQoL and QoL questionnaires may be used to identify aspects of a patient’s health he/she is bothered with. It may be used to monitor the effects of treatment on a patient’s well-being. Moreover, HRQoL and QoL assessment may provide opportunities to apply interventions to improve HRQoL and QoL. Regarding the questionnaires to evaluate HRQoL and QoL in lung cancer: according to the definition of the WHO, no lung cancer specific QoL questionnaire has been developed. Some questionnaires are specifically developed for lung cancer (e.g., EORTC QLQ-C30, FACT-L), although they could be considered as a HRQoL instrument or even a Health Status questionnaire in case of the EORTC QLQ-C30 given the emphasis on physical complaints rather than well-being.

The authors state that the aim of the paper is to evaluate the association of depression symptoms and personality traits with HRQOL. It would help to clarify whether they had a priori hypotheses about direction of these associations, given prior literature, or whether they considered this an exploratory study. It would also help to clarify this in reference to a priori considerations for statistical power.

Response: We thank the reviewer for pointing this out.

Changes to the manuscript:
A priori hypotheses were added to the last section of the introduction.

The following was added to the methods section:
To contribute to statistical power several actions were taken. Firstly, a priori hypotheses were formulated according to the literature that we aimed to test in a homogenous patient population to minimise variability in the outcome measure of interest. Secondly, a recommended rule of thumb was used to calculate sample size (1) and patients were encouraged by the investigators to complete questionnaires to minimise the number of dropouts. Lastly, to minimise the risk for a type I error we applied Benjamini-Hochberg correction to adjust for multiple analyses.

Furthermore, to confirm that the results of our multivariable analyses were supported by sufficient statistical power, we performed a post-hoc power-analysis. Given an alpha of 0.05, a total of no more than nine factors for each multivariable model, and 151 patients, we were able to find an effect size (i.e., partial R2) of 3.98%. This means that the analyses were sufficiently powered to detect factors able to explain at least 3.98% variation in a HRQoL/QoL domain/scale score.


Questions or concerns about the statistical plan: The abstract notes the use of backwards stepwise regression, but this is not addressed in the methods. Recommend explaining rationale for selecting this method with attention to any potential limitations.

Response: We thank the reviewer for her comments on this. The mentioned backwards stepwise regression is wrongfully noted in the abstract and originates from an earlier draft of this manuscript. In the current version of the manuscript backwards regression was not applied. The enter method was used to put all the significant factors remaining from univariable analyses into the multivariable model.

Changes to the manuscript:
The phrase ‘using backwards stepwise selection’ was removed from the method section of the abstract.

The introduction also states that age, PS, gender, education, and marital status have been associated with HRQOL in patients with lung cancer; so it would be helpful for the authors to explain why they selected only age and gender as a priori control variables and tested the remaining factors for statistical significance as the criterion for model entry.

Response: We thank the reviewer for pointing this out. Age and gender were chosen since these are not-modifiable and intrinsic variables. In addition, only in the model that studied the explained variance of social functioning (Table 4) age was later added to the model as it was not identified as potential factor during univariable analysis. However, we agree with the reviewer that this approach is confusing.
Therefore, age and gender, if not identified as a potential predictor in the univariable analysis, were not added to the multivariable models.

Changes to the manuscript:
In the methods section the sentence ‘Subsequently, in a new model…since these variables have been associated with HRQoL’ and the last row of table 4 describing the results of the variable age in the multivariable analyses were deleted.

The authors also note a minimum sample size necessary for model building, which led them to first conduct simple regressions of each predictor and control variable with each outcome. However, it would be helpful to address the large number of analyses. Did the authors consider options for prioritizing or reducing analyses or adjusting for family-wise error?

Response: We thank the reviewer for pointing this out. We repeated our analyses and as a final step applied Benjamini-Hochberg correction to all observed p-values in the multivariable models to adjust for multiple analyses. This resulted in some changes:

Social Relationships: gender and partner status were no longer identified as a predictor.
Environment: CES-D score was no longer identified as a predictor
Global HS/QoL: job status was no longer identified as a predictor
Cognitive Functioning: level of education was no longer identified as a predictor
Social functioning: performance score and partner status were no longer identified as predictors.

Changes to the manuscript:
The corrected P-values were added to tables 3 and 4. The Benjamini Hochberg correction is now added to the statistics section of the Methods.

Might the authors also address the potential overlap of CESD items with psychological items in the QOL measures?

Response: We thank the reviewer for her comment on this. In a study by Da Rocha et al (1) it was demonstrated that after Rasch-analysis only 11 of the 26-items divided over all domains of the WHOQoL-BREF demonstrated differential item functioning regarding the presence of depression. This implies that, while having the same level of quality of life, patients with a depression scored these items differently than those patients without a depression. Moreover, the authors observed just low to moderate correlations (r = -0.13 to r = 0.43) between the CES-D and WHOQoL-BREF domains. This also demonstrates the added value of the WHOQoL-BREF. In addition, one might wonder if addressing this potential overlap of CES-D items with psychological items of the WHOQOL-BREF is justified, given that the constructs behind these questionnaires differ (i.e., CES-D evaluates depressive symptoms, WHOQOL-BREF measures quality of life). Lastly, to correct for this overlap, would possibly imply not relating CES-D score with the Psychological Health domain of the WHOQOL-BREF and with the Emotional and Cognitive functioning domains of the EORTC QQ-C30. However, this would hamper comparing our results with other studies as most studies in cancer do not use an adapted version of the WHOQOL-BREF and EORTC QLQ-C30 (2).

Changes to the manuscript: We added to the last paragraph of the discussion the following:
Third, we related the total CES-D score with HRQoL and QoL. The CES-D contains some items that may demonstrate an overlap with the domains/scales of the WHOQoL-BREF and EORTC QLQ-C30. This could partly explain the observed associations between CES-D score and these domains/scales.
However, it was previously demonstrated that just low to moderate correlations exist between the CES-D and the WHOQoL-BREF (Rocha). Moreover, in the same article results of a Rasch-analysis were reported that demonstrated that just 11 items of the WHOQoL-BREF demonstrated differential item functioning regarding the presence of depression meaning that at a same level of QoL patients with a depression scored these 11 items differently than those without a depression. Removing these 11 items from our analyses would hamper comparing our results with other studies as most studies in cancer do not use an adapted version of the WHOQOL-BREF. In addition, given that the constructs of these questionnaires differ, this also contributes to their utility apart from each other.


I recommend attending to clinical generalizations in the discussion, such as '(HR)QOL management is mandatory in patients with poor prognosis”, or "physician awareness of depression symptoms…could stimulate early referral to a psychologist,” given current national and regional guidelines and common available resources at cancer centers.

Response: We thank the reviewer for pointing this out.

Changes to the manuscript:
These phrases were deleted during the revision process from the first section of the discussion.

At the same time, it would be helpful to have more attention to placing current results in context of existing research and next steps, including observational or intervention research in lung and other related cancers. Given the number of analyses, it may be challenging to synthesize the results while having space to interpret them, but I felt it was somewhat confusing to have the discussion report on new follow-up analyses that were not addressed in the methods and results. The paragraphs that summarized the main results attended mainly to the statistical explorations, but the authors may consider how to strike more of a balance between those and implications.

Response: We thank the reviewer for pointing this out. In the discussion section we added a paragraph that puts our observations into the context of the existing literature.

Changes to the manuscript: the following section was added to the discussion:
Compared to a recent study in Dutch patients with lung cancer, we observed a lower general health/QoL score (i.e., facet score of 7.0 (SD 1.4) versus 5.8 (1.7) in this study) (1). Probably this is due to the inclusion of solely patients with locally-advanced and metastatic lung cancer in our study whereas the referred study included patients with all stages of lung cancer with stage I and II comprising 45% of the study population. However, this difference in QoL underscores the need for the development of interventions to improve QoL in patients with advanced-stage lung cancer. In patients with breast and prostate cancer, it was reported that an easy-to-use well-being intervention (i.e., recording of positive experiences in a diary, listening to a mindfulness CD, planning a pleasurable activity) could positively influence overall QoL (i.e., facet score WHOQoL-BREF) (2). Moreover, in a study with Iranian breast cancer patients an intervention of eight mindfulness group-based training sessions resulted in improved overall QoL and less depressive symptoms, anxiety, and stress compared
to the control group (3). Regarding HRQoL, a Cochrane review reported that exercise training resulted in improved global HRQoL although this was not observed for physical functioning (4). However, the risk of bias in all six included studies was high and the quality of evidence for the outcomes was low. In another study Nabilone, a synthetic cannabinoid used to improve caloric intake, resulted in improved aspects of HRQoL (i.e., role functioning, emotional functioning, and social functioning) (5). Unfortunately, all of the mentioned studies are hampered by their design and relatively small sample sizes, although their results suggest that the development of interventions to improve HRQoL and QoL could be beneficial for patients with advanced-stage cancer. Therefore, randomized studies with larger patient populations are needed that could further develop and test the additional value of interventions designed to improve HRQoL and QoL. Such studies should particularly aim their proposed interventions at improving performance status and depressive symptoms as, according to our results, these factors contribute the most to HRQoL and QoL.


Introduction
Were the data collected specifically for the current study? If not, what were the aims of PERSONAL and how did the current study aims fit into those? I recommend clarifying this in the text.

Response: We thank the reviewer for pointing this out.

Changes to the manuscript:
Under study population we added: The present study is part of PERSONAL. PERSONAL aims to study the pharmacokinetic and pharmacologic effects of pemetrexed. In addition, patient reported outcomes are measured.

Methods and results
Would be helpful to include more information about study procedures. How were the current study measures administered? How was study eligibility confirmed? What was the source of the sociodemographic and clinical data that were collected for the study? Under clinical information, it would help to clarify what is meant by 'history' or how 'disease response' was measured. How was the
NEO-FFI scored -raw scores used or transformation into T-score?

Response: We thank the reviewer for this comment. These points are added to the section that describes the NEO-FFI, study population and the last section of the section study measures. We used the raw-scores of the NEO-FFI. Regarding the variable disease response, we choose to not describe this variable in Table 1 as the variable was not used for the analyses. The present study reflect on the period just before and during the first day of treatment. Disease response of patients is obviously not known at that time. This is also a reason why we choose to not report this variable.

Changes to the manuscript:
Under ‘study population’ we added:
‘The present study is part of PERSONAL. PERSONAL aims to study the pharmacokinetic and pharmacologic effects of pemetrexed. In addition, patient reported outcomes are measured.’

‘Eligibility was checked by two physicians dedicated to the project.’

We added a new section to the methods:
‘Procedures
All questionnaires were administered during consultations or by mail and completed after diagnosis and just before or at the first day of the first cycle of chemotherapy. In addition, we collected sociodemographic information (i.e., age, gender, educational level, ethnicity, employment, partner status) and clinical information (i.e., cancer stage, type of tumour, line of therapy, and the Eastern Cooperative Oncology Group (ECOG) performance status) from the hospital electronic information records and during regular consultations.’

Tables 3 and 4 may be showing only the regression predictors that had statistically significant associations with the outcomes, and perhaps this is related to running backwards selection, but to fully understand which variables were tested in each model, the reader might have to review numerous online supplemental simple regression tables. The authors might consider other ways to present information about the models that were run.

Response: We thank the reviewer for pointing this out. As mentioned earlier we used the enter method to put all the significant factors remaining from univariable analyses into the multivariable model. In the methods section we describe the variables used for the univariable regression analysis for each dependent variable (i.e., WHOQoL-BREF and EORTC QLQ-C30 domains/scales). To provide more information regarding the univariable analyses we added a table that describe the results of the univariable analyses.

Changes to the manuscript:
We added a table to the manuscript describing the results of the univariable analyses.

I suggest clarifying support for using the CES-D in cancer, given the neurovegetative symptoms that could overlap with cancer and cancer treatment-related symptoms.

Response: We thank the reviewer for pointing this out. The present study is part of a larger study, i.e. PERSONAL. Patients of this project completed a pre-determined set of questionnaires. Given that the present study is part of this project, only CES-D scores were available to assess the relation between (HR)QoL and depressive symptoms. Moreover, it has been previously reported that evidence for
removing somatic items from the CES-D in cancer patients could not be confirmed (1). In addition, the
used version of the CES-D in the present study contains just one item that may be perceived to reflect a
neurovegetative symptom, i.e. anorexia. Lastly, the CES-D is commonly used in studies exploring
depressive symptoms in cancer patients.

Changes to the manuscript: To clarify our choice for the CES-D we added to the paragraph describing
the limitations in the discussion section:
‘Fourth, the CES-D also contains some items that demonstrate an overlap with physical symptoms of
cancer patients. In potential, this could also partly explain the observed associations between CES-D
score and HRQoL and QoL. However, in a study evidence for removing somatic items from the CES-D
in cancer patients could not be confirmed (1). In addition, the definition of depressive symptoms
includes symptoms like weight loss and fatigue besides symptoms associated with a negative affect.
Moreover, to not include the scores of the somatic items in the total CES-D score, would hamper
comparing our results with other studies as many studies in cancer use a total CES-D score.’

symptoms with the CES-D to assess depression in cancer patients after treatment: comparison among
patients with oral/oropharyngeal, gynecological, colorectal, and breast cancer. Psychosomatics. Nov-

The authors note that the CES-D and the NEO-FFI both have good psychometric properties, but it
would help to clarify and cite which populations were used to establish the properties that they are
referring to.

Response: We thank the reviewer for pointing this out.

Changes to the manuscript:
Populations in which the psychometric characteristics of the CES-D and the NEO-FFI have been
evaluated were added to the corresponding paragraphs in the method section.

Discussion

Both the introduction and the discussion state that significant treatment side effects and adverse events
impact QOL in patients, but it could be made clearer that the study focused on patients who had not yet
started treatment (except possibly for those on second line treatment).

Response: We thank the reviewer for pointing this out.

Changes to the manuscript:
We added ‘prior to or at the start of treatment’ in the introduction and discussion, given that a
considerable proportion of patients completed the questionnaires not only before but also at day 1 they
received the first course of chemotherapy.

Minor points

The authors use an acronym (HR)QOL that might be referring to both HRQOL and QOL
simultaneously. As this is not a common notation and may not reflect the authors stance that QOL and
HRQOL are distinct constructs, it may help to avoid using it.

Response: We thank the reviewer for this comment. It is correct that with (HR)QoL both HRQoL and
QoL are meant.

Changes to the manuscript:
We changed this to HRQoL and QoL throughout the manuscript.

With respect to the minimal missing data observed in the study, I wasn't sure why the number of patients who completed the questionnaires, as shown in Figure 1, was higher than the sample sizes used to calculate the mean scores on the questionnaire subscales.

Response: We thank the reviewer for pointing this out. This is the result of the fact that some patients did not complete the minimal number of items of some domains/scales to result in a domain/scale score. However, still at least 89% of patients completed all domains of all questionnaires.

Changes to the manuscript:
In the results section, we added: ‘89% of patients completed all domains of all questionnaires.’

Ping Yang (Reviewer 2):

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).

Response: We thank the reviewer for this comment.

Changes to the manuscript:
The title was changed to: 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

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.

Response: Results of the present study provide additional information given that also analyses were performed that related depressive symptoms, personality traits, and clinical variables with QoL besides HRQoL. Moreover to our knowledge no studies have been reported that investigated the association between personality traits and HRQoL/QoL in patients with lung cancer.

In the discussion section we explored the reason for non-significance of the NEO-FFI personality traits. It was expected that their effect could be masked by CES-D score but this was not the case. Moreover, previous studies discussing such a relationship in cancer or other diseases have not been reported. However, earlier type D personality has been related with HRQoL.
Changes to the manuscript: we added the following sentence to the paragraph that discusses the negative relation between the NEO-FFI and HRQoL and QoL:

In contrast, type D personality has previously been related with decreased HRQoL in patients with cancer (1,2). Given that in the past type D personality has been positively correlated with neuroticism and negatively with extraversion in healthy individuals (3,4) it remains unclear why neuroticism or extraversion were not related with HRQoL or QoL in the present study. A reason for this may be that type D personality is more related with HRQoL and QoL than the NEO-FFI personality traits as was observed in female patients with ulcerative colitis (4). Unfortunately, other studies that could further elucidate this lack of significance between NEO-FFI personality traits and HRQoL and QoL in cancer patients have not been reported. Therefore, the effect of personality traits according to the NEO-FFI on HRQoL and QoL remains unclear in patients with lung cancer.


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)

Response: We thank the reviewer for mentioning these points. Throughout the paper these points were addressed.

Changes to the manuscript:
A: A reference was added and the sentence was changed to: … treatment may be associated with considerable side effects, which can directly influence Health-Related Quality of Life (HRQoL) (1) or
even QoL in patients with metastatic cancer.

B: This sentence was changed to: Contemplating on these considerations, we aimed to evaluate to which extent depressive symptoms and personality traits solely and among variables related to HRQoL are associated with HRQoL and QoL in patients with advanced-stage lung cancer prior to or at the start of treatment.

C: This sentence replaced by: ‘We expected depressive symptoms to be associated with lower scores on HRQoL and QoL. In addition, we estimated neuroticism and trait anxiety to be associated with decreased HRQoL and QoL scores.

D: This sentence was changed to: Openness reflects to an open attitude towards experiences, beliefs and, people (raw score ≥41). Agreeableness relates to orientation in other people’s experiences, goals and interests (raw score ≥ 49).

E: This sentence was changed to: Figure 1 demonstrates the selection of patients.

F:This sentence was changed to: With the variables associated with the WHOQOL-BREF domains and EORTC QLQ-C30 scales according to the simple linear regression analyses, multiple linear regression analyses were performed.

G: This sentence was changed to: Considering that HRQoL merely reflects those components of QoL that are influenced by treatment and disease [33], we choose to include a QoL measure (i.e., WHOQOL-BREF) as well since this offers additional information describing patients’ feelings about their well-being including their environment and spirituality/existentiality.

H: this sentence was changed to: we hypothesized whether the absent effect of NEO-FFI personality traits on HRQoL and QoL was influenced by CES-D score. Therefore, new analyses were performed without using CES-D score as a potential predictor in the multivariable analyses.


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.

Response: We thank the reviewer for this comment.

Changes to the manuscript: the background section of the manuscript was changed to:

‘Background: Identification of patient-related factors associated with Health-Related Quality of Life (HRQoL) and Quality of Life (QoL) at the start of treatment may identify patients who are prone to a decrease in HRQoL and/or QoL resulting from chemotherapy. Identification of these factors may offer opportunities to enhance patient care during treatment by adapting communication strategies and directing medical and psychological interventions. The aim was to examine the association of sociodemographic factors, personality traits, and depressive symptoms with (HRQoL and QoL in
patients with advanced-stage lung cancer at the start of chemotherapy.

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).

Response: We thank the reviewer for pointing this out.

Changes to the manuscript:
We categorized the measures.

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., \( p \leq 0.05 \)).

Response: We thank the reviewer for pointing this out.

Changes to the manuscript:
We added ‘a \( P \leq 0.10 \) was used to prevent non-identification of important factors’ and also added ‘\((P \leq 0.05)\)’ at the end of the method section of the abstract.

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

Response: We thank the reviewer for pointing this out.

Changes to the manuscript:
We added the following to the results section of the abstract: Personality traits were not related with HRQoL or QoL, except for trait anxiety (Role functioning: \( \beta = 0.30; P = 0.009 \), Environment: \( \beta = -0.39; P = 0.001 \)) and conscientiousness (Physical health: \( \beta = 0.20; P\text{-value} < 0.016 \)).

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?

Response: We thank the reviewer for this comment.

Changes to the manuscript:
We deleted ‘earlier’ and at the end of the sentence added in the past decades.

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.

Response: We thank the reviewer for pointing this out.

Changes to the manuscript: A new section was added to the introduction that further discusses these differences:
HRQoL focusses on health and represents the impact of disease and treatment on the feelings patients have about their functional capabilities and well-being [1]. QoL assesses patients’ feelings (i.e.,
satisfied or bothered) about their functioning and well-being in at least three key areas (i.e., physical, psychological and social well-being). It also evaluates a patient’s feelings related to their environment (e.g., satisfaction with living conditions) or spirituality (e.g., meaningfulness of personal life). A recent study underscores the additional value of spirituality for a patient’s well-being as it observed that better cognitive and emotional functioning was seen in cancer patients with higher spiritual well-being (2). Patients with better global Health Status/QoL also had higher spiritual well-being. In addition, besides the additional assessment of a patient’s environment and spirituality, a QoL instrument also contains positively phrased items.

In studies that investigate new therapies in lung cancer, often HRQoL is evaluated and not QoL. These studies evaluate HRQoL to determine the impact of treatment on cancer patients’ well-being. QoL may be used in a similar manner and provides further information as it enables a more comprehensive assessment of a patient’s well-being than HRQoL. In a clinical setting, application of HRQoL and QoL questionnaires may be used to identify aspects of a patient’s health that he/she is bothered with. It may be used to monitor the effects of treatment on a patient’s well-being. Moreover, HRQoL and QoL assessment may provide opportunities to apply interventions to improve HRQoL and QoL. Regarding the questionnaires to evaluate HRQoL and QoL in lung cancer: according to the definition of the WHO, no lung cancer specific QoL questionnaire has been developed. Some questionnaire are specifically developed for lung cancer (e.g., EORTC QLQ-C30, FACT-L), although they could be considered as a HRQoL instrument or even a Health Status questionnaire in case of the EORTC QLQ-C30 given the emphasis on physical complaints rather than well-being.

Throughout the manuscript we separated HRQoL and QoL from each other.

Further, the specific value of assessing "additional concepts, such as the environment and spirituality" could be elaborated upon with literature underscoreing the previously established importance of these concepts in relation to depressive symptoms and how they impact "a patient's well-being."

Regarding the additional value of the environment and spirituality on HRQoL/QoL in relation to depressive symptoms, a recent study by Abou Chaar and colleagues observed that better cognitive and emotional functioning was seen in cancer patients with higher spiritual well-being (2). Patients with better global Health Status/QoL also had higher spiritual well-being. Anxiety and depressive symptoms were negatively associated with spiritual well-being.

Changes to the manuscript: we added to the second paragraph of the introduction of the revised manuscript the following:
A recent study underscores the additional value of spirituality for a patient’s well-being as it observed that better cognitive and emotional functioning was seen in cancer patients with higher spiritual well-being (2). In addition, patients with better global Health Status/QoL also had higher spiritual well-being.

Moreover, the following sentence of the third paragraph of the revised manuscript was changed from ‘Investigating the association between these factors and QoL may provide further information about the
relation between them and a patient’s well-being.’ to ‘However, given that depressive symptoms have
been negatively associated with spiritual well-being (2), investigating the association between
depressive symptoms and QoL may provide further information about the relation between depressive
symptoms and a patient’s well-being.’

Orthopaedie 21 (2):39-42
depression among patients with cancer: an observational transversal study. Supp Care Cancer 26 (8):
2581-2590

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?

Response: We thank the reviewer for pointing this out. We think there may be indeed additional value in assessing personality traits besides directly evaluating (HR)QoL. Reason for this is that personality traits are linked with coping mechanisms. For instance, patients that score high on neuroticism tend to use ineffective coping strategies. Therefore, knowing which personality traits a patient has may help health care professionals direct their care and communication in a personalized manner that responds to the patient’s personality traits. In addition, personality may also be considered upon making treatment decisions.

In a study with patients with breast cancer, women that scored high on trait anxiety had lower QoL when they chose breast conserving surgery instead of mastectomy (1).

Although it remains the question to what extent and if personality traits are modifiable, taking knowledge of patient personalities may help personalize communication strategies and the manner in which care is delivered. This may for instance be of importance regarding coping strategies and treatment adherence.

Changes to the manuscript: We added to the paragraph ‘Personality has been associated … HRQoL
and/or QoL’ the following sentences:
Moreover, taking knowledge of patients personality traits may be of importance as they are linked with coping mechanisms. It may help personalize communication strategies and the manner in which supportive care is delivered. This may be of importance to increase, for instance, treatment adherence.

negative impact on quality of life after breast-conserving therapy. World J Surg. Jul;34(7):1453-60. doi:
10.1007/s00268-010-0526-0.

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.
Response: We thank the reviewer for his comment.

Changes to the manuscript:

The title was changed (see above under major issue point 1)

The last paragraph of the introduction was changed to reflect the complete list of factors that were investigated:

Contemplating on these considerations, we aimed to evaluate to which extent depressive symptoms and personality traits solely and among variables related with HRQoL (i.e., age, performance status, gender, education, and having a spouse [4-6]) are associated with HRQoL and QoL in patients to advanced-stage lung cancer prior to or at the start of treatment. We expected depressive symptoms to be associated with lower scores on HRQoL and QoL. In addition, we estimated neuroticism and trait anxiety to be associated with decreased HRQoL and QoL scores.

In the first paragraph of the discussion the sentence ‘To our knowledge, this prospective multi-centre observational study is the first that aimed to investigate the association of personality traits and depressive symptoms with HRQoL and QoL in patients with advanced-stage lung cancer prior to or at the start of treatment’ was changed to ‘To our knowledge, this prospective multi-centre observational study is the first that aimed to investigate the association of personality traits, depressive symptoms, and sociodemographic variables with HRQoL and QoL in patients with advanced-stage lung cancer prior to or at the start of treatment.’

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.

Response: We thank the reviewer for addressing this point. Only 10 patients with mesothelioma (i.e., 6.6% of the total patient population) were used in the analysis. Given that mesothelioma patients received the same chemotherapy as the other patients, we did not expect differences in terms of number and severity of adverse events. Moreover, prognosis in patients with mesothelioma is also limited. Given these similarities between patients with mesothelioma and NSCLC it is not expected that leaving the 10 patients out of the analyses would result in different results than the observed ones. To check for this assumption, we performed the multivariable analysis without the patients with mesothelioma. We observed that regarding the facet score of the WHOQoL-BREF neuroticism was identified as an additional predictor. However after application of Benjamini-Hochberg correction this factor was not longer significant. Regarding physical health, after application of Benjamini Hochberg correction conscientiousness was no longer identified as a predictor. Probably, these differences are the result of the smaller sample size.

Changes to the manuscript: we added the following to section in the discussion that describes the limitations:
For this reason, the ten patients with mesothelioma (i.e., 6.6% of the total patient population) were also used for the analysis. Given that the mesothelioma patients received the same chemotherapy as the
other patients, we did not expect differences in terms of number and severity of adverse events between the mesothelioma and the lung cancer patients. Moreover, prognosis in patients with mesothelioma is also limited. Therefore, considering these similarities it was expected that the use of the data of the 10 patients for our analyses would not interfere with the observations of this study. To verify his assumption, the multivariable analysis were rerun without the 10 mesothelioma patients. After Benjamini-Hochberg correction, we observed the same results except that conscientiousness was no longer identified as a predictor of physical health.

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.

Response: We thank the reviewer for pointing this out. Only 11 patients received second line treatment. We expect this group to be too small to have a decisive impact on the obtained results. To verify this assumption, we performed univariable analyses with line of therapy (i.e., first line or second line) as a factor of the WHOQoL-BREF domains and EORTC QLQ-C30 scales. Line of therapy was only identified as a possible factor of the facet score of the WHOQoL-BREF and the global QoL/HS and emotional functioning scales of the EORTC QLQ-C30 (P ≤ 0.10). Subsequently, multivariable analyses including line of therapy as a factor were performed for the facet and the two scales. In none of the three analyses line of therapy was identified as a factor (P ≤ 0.05). Given that line of therapy was not identified as a significant factor in the multivariable analyses and the fact that we aimed to focus on demographic and personality related variables, we choose not to correct for this covariate. Moreover, other tumor/treatment related factors were also not included in the analyses.

Changes to the manuscript:
We moved the final paragraph of the study measures section after study population and called it Procedures.

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)?

Response: We thank the reviewer for this comment. Relatives could indeed help a patient complete the questionnaires. However, only if patients were able to comprehend the questions. Zero patients were excluded, because everyone was able to understand the questions.

Reasons for non-completion of questionnaires are not known. Participants do not need to inform the researchers about these reasons. It is expected that the stress levels patients experienced due to the treatment, diagnosis of cancer prohibited completing the questionnaires. This information was added to the results section.
Changes to the manuscript: the following sentence was added:
‘In general, reasons for non-completion of questionnaires were related to the stress patients experienced resulting from a diagnosis of advanced-stage lung cancer, the near start of chemotherapy, and a poor prognosis.’

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).

Response: We thank the reviewer for his comment.

Changes to the manuscript:
Examples of items were added.

WHOQoL-BREF: Examples of items are: How satisfied are you with your capacity for work? (physical health), How safe do you feel in your daily life? (psychological health), How satisfied are you with your personal relationships? (social relationships), How satisfied are you with your transport?

EORTC QLQ-C30: Examples of items are: Do you have trouble taking a long walk? (physical functioning), Have you had difficulty remembering things? (cognitive functioning), Did you feel depressed? (emotional functioning), Has your physical condition or medical treatment interfered with your family life? (role functioning), Has your physical condition or medical treatment interfered with your social activities? (social functioning).

STAI: An example of an item is: I worry too much over something that really doesn’t matter.

NEO-FFI: Examples of items are: I often feel inferior to others (neuroticism), I laugh easily (extraversion), Once I find the right way to do something, I stick to it (openness), I try to be courteous to everyone I meet (agreeableness), I keep my belongings clean and neat (conscientiousness).

CES-D: I felt that people dislike me.

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?"

Response: We thank the reviewer for pointing this out.

Changes to the manuscript:
Response is changed for QoL.

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.
Response: We thank the reviewer for pointing this out. If possible, we referred to studies that assessed the psychometric properties in patients with lung cancer. For instance the validation study of the EORTC QLQ-C30 by Aaronson et al was carried out with lung cancer patients. Also we cite a study by Lin et al that reported on the psychometric properties of the WHOQOL-BREF in lung cancer. If the psychometric properties of a certain questionnaire were not investigated in lung cancer patients, we added the population in which it was assessed. In addition, in other studies using these instruments similar descriptions of these instruments are provided. Moreover, mentioning all specific psychometric properties of the instruments (i.e., internal consistency, construct validity, etc) would go beyond the intention of the particular paragraphs.

Changes to the manuscript:
We added ‘relatively low Cronbach’s alpha < 0.70’ to the last sentence of the paragraph discussing the WHOQOL-BREF.

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

Response: We thank the reviewer for his comment on this.

Changes to the manuscript:
We replaced several items with 13 items.

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

Response: We thank the reviewer for pointing this out. The 10-item trait anxiety subscale was chosen to assess anxiety as it has been developed and validated in the Dutch population (1). Moreover, we choose the 10-item trait anxiety subscale to reduce time and effort required of severely ill patients already involved in extensive assessment procedures. In addition, the present study is part of a larger study, i.e. PERSONAL. Patients of this project completed a pre-determined set of questionnaires. Given that the present study is part of this project, only scores of the 10-item STAI trait anxiety scale were available to assess the relation between HRQoL/QoL and trait anxiety.


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?

Response: We thank the reviewer for his comment on this. The present study is part of a larger study, i.e. PERSONAL. Patients of this project completed a pre-determined set of questionnaires. Given that the present study is part of this project, only CES-D scores were available to assess the relation between (HR)QoL and depressive symptoms. However, it has been previously reported that evidence for removing somatic items from the CES-D in cancer patients could not be confirmed (1). Moreover, previous studies have demonstrated that physical symptoms are a risk factor for depression in patients with cancer. Also, the definition of depression includes symptoms like weight loss and fatigue besides symptoms associated with a negative affect. Lasly, to address for this overlap, could mean leaving the
score of the items that refer to somatic symptoms out of the total ces-d score. In our models we used total ces-d. To not include the scores of the somatic items in total CES-D score, would hamper comparing our results with other studies as most studies in cancer exploring depressive symptoms use a total CES-D score.

Changes to the manuscript: To clarify our choice for the CES-D we added to the paragraph describing the limitations in the discussion section:

‘Fourth, the CES-D also contains some items that demonstrate an overlap with physical symptoms of cancer patients. In potential, this could also partly explain the observed associations between CES-D score and HRQoL and QoL. However, in a study evidence for removing somatic items from the CES-D in cancer patients could not be confirmed (1). In addition, the definition of depressive symptoms includes symptoms like weight loss and fatigue besides symptoms associated with a negative affect. Moreover, to not include the scores of the somatic items in the total CES-D score, would hamper comparing our results with other studies as many studies in cancer exploring depressive symptoms use a total CES-D score.’


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.

Response: We thank the reviewer for his comments.

Changes to the manuscript:

‘Neuroticism measures emotional stability, while extraversion assesses the level to which orientation, energy and attention are focused on the outside world instead of the inner world. Openness reflects to an open attitude towards experiences, beliefs and, people, whereas agreeableness relates to orientation in other people’s experiences, goals and interests’…

…was changed to ‘Neuroticism measures emotional stability. Extraversion assesses the level to which orientation, energy and attention are focused on the outside world instead of the inner world. Openness reflects to an open attitude towards experiences, beliefs and, people. Agreeableness relates to…

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.

Response: We thank the reviewer for mentioning this.

Changes to the manuscript:
‘Agreeableness relates to orientation in other people’s experiences, goals and interests’…

…was changed to ‘Agreeableness relates to a person’s level of being empathic, cooperative, and considerate.’
‘Conscientiousness refers to the conscience as a guiding and reflective instrument for behavior’…

… was changed to ‘Conscientiousness refers to the level of being careful, diligent, and orderly.

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?

Response: We thank the reviewer for these comments.

The number of predictors for the univariable analyses (m) were fourteen. We selected them based on previous research. The aim of this study was to assess the impact of personality traits, depressive symptoms, and demographic and other patient related factors (age, gender, ECOG status) on HRQoL and QoL, not the effect of clinical factors such as smoking status, history, cancer stage, disease response, etc. Given the aim of the study and the relatively small sample size of 151 patients, we omitted these variables from the analyses. By not doing so we would risk ending up with models that contained too much variables relative to our sample size. Therefore the information of these variables was provided as background information.

Age and gender were chosen since these are not-modifiable and intrinsic variables of patients. However, we agree with the reviewer that this approach is confusing. Therefore, age and gender, if not identified as a potential predictor in the univariable analysis, were not added to the multivariable models. As such, age and gender were handled in a similar manner during the analyses as partner status and education.

Changes to the manuscript:
In the method section, smoking status was removed as a variable and marital status rewritten as partner status. In the results section, we changed sex to gender and added employment, partner status, and cancer stage.

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

Response: We thank the reviewer for his comment.

Changes to the manuscript:
In the method section, smoking status was removed as a variable and marital status rewritten as partner status. In the results section, we changed sex to gender and added employment, partner status, and cancer stage.
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

Response: We thank the reviewer for his comment.

Changes to the manuscript:
In the methods section the list of clinical information was changed to cancer stage, type of tumour, line of therapy, and the Eastern Cooperative Oncology Group (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.

Response: We thank the reviewer for this comment.

Changes to the manuscript:
A column describing the range of the scale/domain scores was added.

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?

Response: We thank the reviewer for pointing this out. What is meant is that the association between CES-D score and environment the weakest of the observed associations was.

Changes to the manuscript:
The sentence: ‘Moreover, for both WHOQOL-BREF and EORTC QLQ-C30 domains/scales, except for environment, the association with CES-D score was the strongest’ was removed and replaced with ‘All of the standardized betas for the association between CES-D score and the domains/scales of the WHOQOL-BREF and EORTC QLQ-C30 were larger than 0.40 except for the association between CES-D score and environment.’

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?

Response: We thank the reviewer for his comment.

The term backwards selection as mentioned in the abstract dates from an earlier version of the manuscript. For the current version multivariable analyses were performed by using the ENTER method.

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).

Response: we thank the reviewer for pointing this out.

Changes to the manuscript: we changed the corresponding sentence of the first paragraph of the discussion:
To our knowledge, this prospective multi-centre observational study is the first that aimed to investigate if personality traits, depressive symptoms, and sociodemographic factors are associated with HRQoL and QoL in patients with advanced-stage lung cancer prior to or at the start of treatment.

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.

Response: We thank the reviewer for pointing this out. The observed effect of trait anxiety in the absence of depressive symptoms is of importance as it may provide professionals opportunities to personalize the way they provide supportive care (e.g., by adapting communication strategies, stimulating effective coping mechanisms).

We searched the literature for studies that associated/correlated trait anxiety with QoL and HRQoL. No reports were found that related trait anxiety with QoL. Regarding HRQoL, in a study with Turkish colorectal patients that receive chemotherapy patients with low trait anxiety (scale score < 45) had better HRQoL for all EORTC QLQ-C30 functioning scales and the global QoL/HS scale (1). However, depressive symptoms were not used as a covariate in their analysis. Another study in women under follow-up for breast cancer observed that the level of anxiety according to the State-Trait Anxiety Inventory was related with the emotional functioning scale of the EORTC QLQ-C30 (2). These results put the results of our analyses into context and strengthens them.

Changes to the manuscript: the sentence ‘These results emphasize the importance of trait anxiety, especially in the absence of depressive symptoms’ was replaced for …

‘Previously, similar results have been observed. In a study with Turkish colorectal patients that received chemotherapy, patients with low trait anxiety (scale score < 45) had better HRQoL for all EORTC QLQ-C30 functioning scales and the global QoL/HS scale (1). Another study in women under follow-up for breast cancer observed that the level of anxiety according to the total STAI score was related with the emotional functioning scale of the EORTC QLQ-C30 (2). As such, our observations and the results of these studies emphasize the importance of trait anxiety as a factor associated with HRQoL and QoL, especially in the absence of depressive symptoms and may provide professionals opportunities to personalize the way they provide supportive care (e.g., by adapting communication strategies, stimulating effective coping mechanisms).’

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.

Response: we thank the reviewer for pointing this out.

Changes to the manuscript:
the sentence ‘Therefore, the effect of personality (i.e., except for trait anxiety) on (HR)QoL may be less important in patients with lung cancer ‘ was changed to ‘Therefore, the effect of personality traits according to the NEO-FFI on HRQoL and QoL remains unclear in patients with lung cancer.

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

Response: We thank the reviewer for these comments. Reviewer 1 suggested to correct the observed results for the multiple analyses that were performed. Therefore, applied Benjamini-Hochberg correction to the observed p-values in the multivariable models.
   a) after Benjamini Hochberg correction was applied CES-D score was no longer significantly related with Environment besides Social Relationships
   b) after Benjamini Hochberg correction was applied CES-D score was no longer significantly related with Environment.

Changes to the manuscript:
We added to the discussion: In the present study CES-D score was related to all HRQoL scales and QoL domains, except the WHOQoL-BREF domains social relationships and environment. Previously, the CES-D score has been related with HRQoL and QoL in breast cancer (1,2). In the study by Hyphantis and colleagues, amongst others, age, stage of cancer, levels of anxiety, depressive symptoms, and use of repression were related with QoL (2). In line with the results of the present study, they did not observe a relationship between social relationships and CES-D score. However, in another study in lung cancer patients significant depressive symptoms were associated with decreased QoL, including social relationships and environment (3). Reasons for this may be related to differences in patient characteristics or the relatively large time (i.e., at least 20 months) since diagnosis that patients completed the questionnaires compared to our study. In our study, patients were at the start or prior to treatment whereas in study by Gu et al. patients already received treatment for some time. Treatment may have had an impact on the relation between depressive symptoms and QoL.


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.

Response: we thank the reviewer for pointing this out

Changes to the manuscript: we added the following to this paragraph:

This is in contrast with previous results. In a study with patients with chronic diseases trait anxiety was negatively associated with role physical and role emotional score of the Short-Form 36, a HRQoL questionnaire (1). Moreover, in colorectal survivors anxiety was significantly associated with lower role functioning over time (2).

The sentence ‘Moreover, the alternative explanation, i.e., the positive direction of the beta is a true observation, seems rather unlikely.’ was deleted.

We also added:
However, in a study with advanced-stage cancer patients a similar result was observed [4]. Another study reported also lower social functioning in married/cohabited patients [5]

We also deleted: ‘Therefore, the direction of this beta may be a true observation, or just the effect of another variable that was not included in the analysis (i.e., a confounder). If partner status would be highly correlated with this confounding variable, this could switch the direction of the beta in the expected direction. Other reasons for the observed unexpected results may be that they are merely due to chance (i.e., especially when there is a small sample size) or are the consequence of selection bias [53].’

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

Response: We thank the reviewer for his comment.

Changes to the manuscript: We added to the last paragraph of the discussion:
Also the application of well-recognized standardized questionnaires, the multi-center prospective design of this study, and the inclusion of patients that resemble clinical practice strengthen our findings.

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.

Response: We thank the reviewer for pointing this out.

Changes to the manuscript: The sentence as changed to:
In conclusion, our results demonstrated that health care professionals are recommended to have high awareness during consultations for patients with depressive symptoms and those with an ECOG performance status of 2 or higher at the start of treatment. This is of importance as these factors may indicate low levels of HRQoL and QoL of patients. Moreover, merely assessing HRQoL and QoL and not depressive symptoms or performance status may not be enough. For instance if psychological health is low, one has to further investigate if this is caused by anxiety or depressive symptoms or another reason given that treatment may differ according to the cause of the low psychological health. Therefore screening for the presence of these two factors before treatment is initiated (e.g., by means of an e-tool that screens for depressive symptoms, consequently reporting performance status during consultations) may be worthwhile. Additional care (e.g., referral to a psychologist, physiotherapist, medication, etc) aimed at improving these factors can then be provided.

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.

Response: We thank the reviewer for addressing these points.

a) Changes to the manuscript:
The conclusion was rewritten (see above)

b) CES-D or another short instrument could be used to screen for depressive symptoms. Such an approach would be less time consuming and less demanding an effort from patients than completing QoL and HRQoL questionnaires which are often more extensive. Furthermore, merely assessing HRQoL and QoL may not be enough. For instance if psychological health is low, one has to further
investigate if this is caused by anxiety or depressive symptoms or another reason given that treatment may differ according to the cause of the low psychological health. Physicians’ awareness could further be increased by emphasizing on depressive symptoms upon taking a patients history by regularly asking if he/she feels depressed. Also providing patients with an e-tool to screen for depressive symptoms before their consultation could be of advantage for physicians to get more insight into this.

Changes to the manuscript:
the conclusion was rewritten (see above)

c) We choose this cut-off as in studies investigating the effect of new therapies mostly patients with a cut-off less than 2 are included. In addition, this cut-off was chosen to clearly discriminate between patients with a relatively good clinical condition and those hampered by a decreased performance status.

d: Studies reporting the course of QoL or depressive symptoms in lung cancer survivors are sparse given the limited prognosis of the disease. Temel et al. (1) demonstrated that early palliative care in these patients improved HRQoL and decreased depressive symptoms. Moreover, in another study by Temel et al. (2) early palliative care resulted in improved HRQoL and depressive symptoms at 12 and 24 weeks after start of treatment in patients with lung cancer. Given the limited prognosis of advanced-stage lung cancer, not intervening results in the prolongation of decreased well-being.

Changes to the manuscript:
We added to the fourth paragraph of the introduction: ‘Moreover, a study by Temel et al. (2) demonstrated that early palliative care in newly diagnosed lung cancer patients improved HRQoL and depressive symptoms at 12 and 24 weeks after treatment commenced’.


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

Response: We thank the reviewer for this comment.

In 2011, a Cochrane review was published describing the effect of non-invasive interventions aimed at improving QoL in patients with lung cancer (1). In this review it was reported that, nurse interventions and interventions to manage breathlessness may have an effect on QoL. Psychotherapeutic interventions could also play a role. Unfortunately, the studies were hampered by bias.

In 2019 a Cochrane review reported that exercise training resulted in improved global HRQoL although this was not observed for physical functioning (2). However, the risk of bias in all six included studies
was high and the quality of evidence for the outcomes was low.

In a recent study by He et al (3) it was observed that resigned acceptance of a diagnosis of lung cancer was negatively associated with Health Status. The authors suggest that adaptive coping could maintain or improve Health Status. Similar results were observed by Nipp et al (4) in incurable cancer patients. Acceptance coping strategies correlated with better HRQoL. They recommended intervention aimed at stimulating an adaptive coping strategy. In another study by Chen et al. (Eur J Cancer Care, 2018) in patients with resected lung cancer, self-efficacy was related with HRQoL. This relation was mediated by fatigue. The study of Ha et al. (Supp Care Cancer, 2018) observed an independent relation of exercise capacity and HRQoL in patients with stage I-IIIA lung cancer who underwent curative treatment.

We advocate to develop specific interventions designed for cancer patients. These interventions should address depressive symptoms, anxiety, and coping style. Methods could be regular consultations for counseling, but also interventions designed to stimulate self-efficacy or improve fatigue or exercise capacity.