

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Predicting postoperative fatigue in surgically treated lung cancer patients in Norway– a longitudinal five-month follow-up study.
AUTHORS	Hugoy, Therese; Lerdal, Anners; Rustoen, Tone; Oksholm, Trine

VERSION 1 – REVIEW

REVIEWER	Carmen P. Escalante, MD University of Texas M D Anderson Cancer Center Houston, TX; USA
REVIEW RETURNED	11-Jan-2019

GENERAL COMMENTS	<p>Review</p> <p>The manuscript is well written. I have the following comments following review:</p> <ul style="list-style-type: none">• Surgery has been shown to attribute much less to cancer-related fatigue (CRF) compared to chemotherapy or radiation treatment. Most patients recover from surgical related fatigue within a few weeks to a month. If it is persistent it may be related to other attributing factors such as lesser optimized comorbidities and symptoms (pain, depression, sleep dysfunction, etc.). It is interesting that you chose to focus on a surgical intervention and then compare it at 5 months post-procedure since residual fatigue at this time period is likely not due to the surgical procedure.• Why did you chose the Lee Fatigue Scale? Although there are many tools to use to measure CRF, this is not one that I have commonly seen utilized in published manuscripts. You used only 13 of the 18 questions. Although the full scale is validated, has it been validated for use of only the 13 questions you chose?• Typo on page 3, under strengths and limitations: “assed”• During the 5 month window for comparison of fatigue, many factors may have occurred that impact fatigue. For example, cancer treatment including chemotherapy, radiation treatment, immunotherapy, etc. In addition, the development of new comorbidities or the exacerbation of known comorbidities. Other symptoms fluctuate over this time frame and influence fatigue. Further, the extent of the malignancy or development of recurrence can affect fatigue changes. How is this accounted for so that fatigue is truly influenced by the surgery and not other effects? Did you collect these factors at any time points other than initial and at 5 months?• The most important question is whether your findings are clinically relevant. I am not sure your conclusion of dyspnea is the predictor of long term fatigue based on your study. Dyspnea may not be due to the lung cancer. Many of these patients have COPD due to tobacco use. Although this may attribute to fatigue, it is not necessarily due to CRF. Further, these findings need to be
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	<p>validated since this can only be considered a derivation model. In addition, it may not be generalizable to other populations.</p> <ul style="list-style-type: none"> • How was missing data (less than 20% missing) handled? • Patients were excluded if they did not have valid fatigue scores. Please clarify. Does this mean they did not have a fatigue score?
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REVIEWER	Bruno Luís de Castro Araujo Hospital do Câncer II, National Cancer Institute of Brazil (INCA), Rio de Janeiro, Brazil.
REVIEW RETURNED	21-Jan-2019

GENERAL COMMENTS	<p>The manuscript refers to a relevant study and fits the scope of the journal. It assesses preoperative predictors of postoperative fatigue in a longitudinal study of surgically treated lung cancer patients. Fatigue is a symptom that has a great impact on quality of life and is frequently neglected in clinical practice. The researchers have used a wide range of well validated questionnaires to evaluate preoperative symptoms and in some follow-up periods.</p> <p>The aim of the study is clear and can be easily captured by reading the title of the manuscript, which is informative and relevant. The abstract synthesises well the paper. Keywords were chosen adequately. The “Strengths and limitations of the study” section could emphasize the strengths of the study. The first three items describe the study itself and the two last describe the limitations. The topic is very relevant to patients and healthcare providers and it could be mentioned there. The introduction summaries clearly what is already known about the topic. The research question is adequately outlined.</p> <p>The methods section defines well the variables and how they were measured. The methods were valid and there is enough detail to replicate the study. The study uses the many validated scales and questionnaires as the Lee Fatigue Scale (LFS), the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire – Lung Cancer Module (EORTC QLQ-LC13), the Center for Epidemiologic Studies – Depression Scale (CES-D), the State-Trait Anxiety Inventory (STAI, Y-2), the General Sleep Disturbance Scale (GSDS), and the Brief-Pain Inventory (BPI). It is not clear in the text if their use was adequately permitted by copyright detectors.</p> <p>In the results section, the sample characteristics and the enrolment process should be detailed. A previous report of the same study included a flowchart of the enrolment in the study. A similar flowchart or a brief description of the enrolment is necessary for a better understanding of the study flow.[1]</p> <p>In Table 1 demographic data stratified by gender was not the best approach in my opinion. It would be better for appraisal if gender was presented by “lines”, not by “columns” of the table. Although table 2 describes an important step in modelling, it may be confusing to the reader and could be suppressed. Table 3 presents the most relevant results of the study. Unadjusted data of these variables could be presented here to clearly show the difference between bivariate and multivariate analysis. The authors should report bivariate analysis related to medical and treatment characteristics in depth, not only as “were not significantly correlated with either preoperative or postoperative fatigue and, thus, were not included in the final model” (p. 11, lines 5-15).</p> <p>The results were discussed satisfactorily, although the subsection “4.2. The relationship between fatigue and patients’ disease</p>
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	<p>characteristics and treatment” should be reassessed for the reasons reported earlier in this review. The sentence “In the present study, treatment and disease variables did not correlate with postoperative fatigue at five-month follow-up” (p. 15, lines 5-11) should ideally be supported by data presented on a table as one of the most important conclusions of the study.[1] The conclusions answered the aims of the study.</p> <p>References are relevant and recent. The reference formatting has some inadequacies according to journal guidelines, which can be checked online (https://authors.bmj.com/writing-and-formatting/formatting-your-paper/).[3] Reference numbers in the text should be inserted immediately after punctuation with no word spacing. Several reference numbers were inserted between two punctuations. The Digital Object Identifier (DOI) should be revised on references 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14, 29, 30, 32, 33, 34, 35, 38 and 39. Date accessed should be inserted at the reference 1 and 37. There is a space after the semicolon on the reference 20.</p> <p>The present report investigates quantitatively associations between some risk factors (preoperative signs and symptoms) and outcomes (preoperative and 5-month follow-up fatigue) longitudinally. Thereby, it should be reported as a cohort study. The correct reporting guidelines to assign is the STROBE and should be cited in the manuscript.[4]</p> <p>Overall, this manuscript describes risk factors for five-month fatigue in surgically treated lung cancer patients. It requires some adjustments, but I believe it is a valuable report that provides interesting insights for future research.</p> <p>References:</p> <ol style="list-style-type: none"> 1. Oksholm T, Rustoen T, Cooper B, et al. Trajectories of symptom occurrence and severity from before through five months after lung cancer surgery. <i>J Pain Symptom Manag</i> 2015;49:995-1015. 2. BMJ Author Hub - Formatting your paper. https://authors.bmj.com/writing-and-formatting/formatting-your-paper/ (accessed 17 Jan 2019). 3. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. <i>BMJ</i> 2007;335:806-8.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

2. Why did you chose the Lee Fatigue Scale? Although there are many tools to use to measure CRF, this is not one that I have commonly seen utilized in published manuscripts. You used only 13 of the 18 questions. Although the full scale is validated, has it been validated for use of only the 13 questions you chose?

Response: We chose The Lee Fatigue scale with 13 items of comparison purposes as we were in a research group that used the same scale. We only used the 13 about fatigue. The last 5 questions is about energy was therefore not included. The psychometric properties of the scale in documented in several other studies, also in cancer patients.

3. Typo on page 3, under strengths and limitations: “assed”

Response: The sentences with the typo is removed

4. During the 5 month window for comparison of fatigue, many factors may have occurred that impact fatigue. For example, cancer treatment including chemotherapy, radiation treatment, immunotherapy, etc. In addition, the development of new comorbidities or the exacerbation of known comorbidities. Other symptoms fluctuate over this time frame and influence fatigue. Further, the extent of the malignancy or development of recurrence can affect fatigue changes. How is this accounted for so that fatigue is truly influenced by the surgery and not other effects? Did you collect these factors at any time points other than initial and at 5 months?

Response: We have checked for treatment and cancer related variables. In order for the reviewer to check the correlation, we have included the results of these correlation analysis in the table below. The findings are discussed in section 4.2. We also collected data at one month but did not add this to the analysis because symptoms shortly after surgery can vary from day to day.

Bivariate values for pre- and postoperative fatigue and treatment and medical variables.

	Preoperative fatigue		Postoperative fatigue	
	Pearsons	P-value	Pearsons	P-value
Stage of cancer	0.13	0.08	0.11	0.16
Cancergroup	0.05	0.48	0.08	0.28
Type of surgery	0.06	0.42	0.01	0.85
Reoperation			-0.07	0.32
Chemotherapy			-0.11	0.12
Radiotherapy			-0.07	0.36

6. The most important question is whether your findings are clinically relevant. I am not sure your conclusion of dyspnea is the predictor of long term fatigue based on your study. Dyspnea may not be due to the lung cancer. Many of these patients have COPD due to tobacco use. Although this may attribute to fatigue, it is not necessarily due to CRF. Further, these findings need to be validated since this can only be considered a derivation model. In addition, it may not be generalizable to other populations.

Response: We do not understand this comment as we do not write that dyspnea is a predictor of long term fatigue. Our findings are encouraging of doing further research in this area.

7. How was missing data (less than 20% missing) handled?

Response: We checked all the instruments if they had more than 20% missing items. The ones with more than 20% missing were excluded from the analyses. If the scales had less than 20% missing, the score were calculated from the mean of the particular patient's valid scores.

8. Patients were excluded if they did not have valid fatigue scores. Please clarify. Does this mean they did not have a fatigue score?

Response: We are sorry for not being clearer. What we meant is that they had to have a valid fatigue scores at both measurement points score to be included in the study. This point is corrected in the manuscript on page 10.

Reviewer 2

1. The "Strengths and limitations of the study" section could emphasize the strengths of the study. The first three items describe the study itself and the two last describe the limitations. The topic is very relevant to patients and healthcare providers and it could be mentioned there.

Response: We have altered the "strength and limitation section" in the study and has increased the emphasize on the strength of the study.

2. The study uses the many validated scales and questionnaires as the Lee Fatigue Scale (LFS), the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire – Lung Cancer Module (EORTC QLQ-LC13), the Center for Epidemiologic Studies – Depression Scale (CES-D), the StateTrait Anxiety Inventory (STAI, Y-2), the General Sleep Disturbance Scale (GSDS), and

the BriefPain Inventory (BPI). It is not clear in the text if their use was adequately permitted by copyright detectors.

Response: We obtained permission to use the questionnaires from the copyright detectors before we started the study. This information is now written into the manuscript.

3. In the results section, the sample characteristics and the enrolment process should be detailed. A previous report of the same study included a flowchart of the enrolment in the study. A similar flowchart or a brief description of the enrolment is necessary for a better understanding of the study flow.

Response: A flow chart is added to the manuscript to give a more detailed description of the inclusions of patients.

4. In Table 1 demographic data stratified by gender was not the best approach in my opinion. It would be better for appraisal if gender was presented by “lines”, not by “columns” of the table.

Response: We have introduced an argument for stratifying variables in table 1 according to sex based in two studies of fatigue in the Norwegian general population, and included sex in the aims and in the results.

5. Although table 2 describes an important step in modelling, it may be confusing to the reader and could be suppressed.

Response: According to the reviewers comment, we have deleted table II and included the bivariate relationships applying standardized beta values in table III (which has become table II in the revised version). The reader will easily see change in the standardized beta values form the bivariate analyses and to the multivariate analyses.

6. Table 3 presents the most relevant results of the study. Unadjusted data of these variables could be presented here to clearly show the difference between bivariate and multivariate analysis.

Response: We agree with the reviewer, and have revised the table accordingly.

7. The authors should report bivariate analysis related to medical and treatment characteristics in depth, not only as “were not significantly correlated with either preoperative or postoperative fatigue and, thus, were not included in the final model” (p. 11, lines 5-15).The results were discussed satisfactorily, although the subsection “4.2. The relationship between fatigue and patients’ disease characteristics and treatment” should be reassessed for the reasons reported earlier in this review. The sentence “In the present study, treatment and disease variables did not correlate with postoperative fatigue at five-month follow-up” (p. 15, lines 5-11) should ideally be supported by data presented on a table as one of the most important conclusions of the study.[1]

Response: The author team has discussed the reviewer’s suggestion including the non-significant findings from the correlation analysis between treatment and pre- and postoperative fatigue in the manuscript. However, we believe that including these numbers is not very informative for the readers. In order for the reviewer to check the correlation, we have included the results of these correlation analysis in the table below. The findings are discussed in section 4.2.

Bivariate values for pre- and postoperative fatigue and treatment and medical variables.

	Preoperative fatigue		Postoperative fatigue	
	Pearsons	P-value	Pearsons	P-value
Stage of cancer	0.13	0.08	0.11	0.16
Cancergroup	0.05	0.48	0.08	0.28
Type of surgery	0.06	0.42	0.01	0.85
Reoperation			-0.07	0.32
Chemotherapy			-0.11	0.12
Radiotherapy			-0.07	0.36

9. References are relevant and recent. The reference formatting has some inadequacies according to journal guidelines, which can be checked online (<https://authors.bmj.com/writing-and-formatting/formatting-your-paper/>).[3] Reference numbers in the text should be inserted immediately after punctuation with no word spacing. Several reference numbers were inserted between two punctuations. The Digital Object Identifier (DOI) should be revised on references 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14, 29, 30, 32, 33, 34, 35, 38 and 39. Date accessed should be inserted at the reference 1 and 37. There is a space after the semicolon on the reference 20.

Response: The reference is checked and is now written according to the journal guidelines. However, we have not been able to find the DOI to reference 12 and 14. The date of accessing is inserted in reference 1 and 37.

10. The present report investigates quantitatively associations between some risk factors (preoperative signs and symptoms) and outcomes (preoperative and 5-month follow-up fatigue) longitudinally. Thereby, it should be reported as a cohort study. The correct reporting guidelines to assign is the STROBE and should be cited in the manuscript.

Response: The STROBE guidelines for a cohort study is used to check the study. The majority of the recommendations from the guidelines was already included in the study. However, a sentence about the study size is included in the beginning of the result section

VERSION 2 – REVIEW

REVIEWER	Bruno Luís de Castro Araujo Hospital do Câncer II, National Cancer Institute of Brazil, Rio de Janeiro, Brazil.
REVIEW RETURNED	15-Jun-2019

GENERAL COMMENTS	<p>The greater part of the adjustments were performed as suggested, but there are some minor necessary remarks.</p> <p>In the results section, Table 1 data could be adjusted to a better appraisal of the results. Better presentation of bivariate analysis would also clarify relevant information to the readers.</p> <p>The references must be reassessed. According to journal guidelines (https://authors.bmj.com/writing-and-formatting/formatting-your-paper/):</p> <p>“Digital Object Identifier (DOI) A DOI is a unique string created to identify a piece of intellectual property in an online environment and is particularly useful for articles that are published online before appearing in print (and therefore have not yet been assigned the traditional volume, issue and page number references). The DOI is a permanent identifier of all versions of an article, whether raw manuscript or edited proof, online or in print. Thus the DOI should ideally be included in the citation even if you want to cite a print version of an article. Find a DOI.</p> <p>* Cite an article with a DOI before published in print: Alwick K, Vronken M, de Mos T, et al. Cardiac risk factors: prospective cohort study. <i>Ann Rheum Dis</i> Published Online First: 5 February 2004. doi:10.1136/ard.2003.001234</p> <p>* Cite an article with a DOI once published in print: Vole P, Smith H, Brown N, et al. Treatments for malaria: randomised controlled trial. <i>Ann Rheum Dis</i> 2003;327:765–8 doi:10.1136/ard.2003.001234 [published Online First: 5 February 2002].”</p>
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	Thereby, the references reporting DOI should be formatted accordingly, as outlined in the previous review.
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

1. In the results section, Table 1 data could be adjusted to a better appraisal of the results.

Response: We are sorry but this is not clear to us. Maybe you can provide more specific information about how you would like to table to look like or what do you want us to change.

2. Better presentation of bivariate analysis would also clarify relevant information to the readers.

Response: Same as above.

3. The references must be reassessed. According to journal guidelines (<https://authors.bmj.com/writing-and-formatting/formatting-your-paper/>). Digital Object Identifier (DOI) need to be altered. Cite an article with a DOI before published in print: Alwick K, Vronken M, de Mos T, et al. Cardiac risk factors: prospective cohort study. *Ann Rheum Dis* Published Online First: 5 February 2004. doi:10.1136/ard.2003.001234

* Cite an article with a DOI once published in print: Vole P, Smith H, Brown N, et al. Treatments for malaria: randomised controlled trial. *Ann Rheum Dis* 2003;327:765–8 doi:10.1136/ard.2003.001234 [published Online First: 5 February 2002].”

Response: We have to apologize for not following the guidelines properly. We have double-checked all the references and have altered the DOI.