Author's response to reviews

Title: Factors associated with the severity and improvement of fatigue in patients with advanced cancer presenting to an outpatient palliative care clinic

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Author's response to reviews: see over
Dated 8.6.12
To
Editor, BMC Palliative Care
Sub: Revised manuscript
Dear Editor,
Attached is the revised manuscript describing “Factors associated with the severity and improvement of fatigue in patients with advanced cancer presenting to an outpatient palliative care clinic.” Based on the reviewers comments we have revised the manuscript and detailed below all changes made in a point-point format as requested.
Best,
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Response to reviewer’s comments:
Reviewer 1
The authors do not give information on the oncological treatments used in the weeks before and after referral to outpatients palliative care clinic, whereas cancer related fatigue is one of the most frequent complications of various anti-tumor therapies. What about the time of referral to the palliative care service? Is a group of patients referred after stopping anti-tumor therapy, thereby causing a decrease of chemotherapy induced fatigue, for example?
Based on the reviewer’s comments we have now clarified the process of referral in the methods section of manuscript (Page 5, para 1): “Most patients referred to the outpatient palliative care clinic receive active cancer treatment including targeted therapy. In all patients fatigue was treated as a multidimensional construct irrespective of whether it was due to disease, cancer treatment or comorbidities.”

The authors mention the retrospective design and the use of a single item instrument as limitations of the study. I agree with that. However, the fact that the ESAS was not always completed by the patients themselves, should also be considered as a limitation. When a nurse or a caregiver helps the patients filling out the questionnaire, scores may differ from scores given by the patient himself. Is bias possible by selective help for the most fatigued patients?
Based on the comments of the reviewer we have revised the methods section of the manuscript to add few sentences to clarify the ESAS administration (Page 6): “In the outpatient settings the vast majority of patients are able to complete ESAS by themselves with minimal assistance.”
In addition in discussion section (page 12, para 2) we have added the following sentences: “Although in the vast majority cases patient complete the ESAS by themselves in outpatient setting there is a possibility that in the most fatigued patients the nurse or caregiver could have introduced the bias by assisting the patient. More research is necessary to address this possibility.”
The authors did not study “if changes in fatigue were related to changes in the severity of other ESAS scores …to strongly imply causal relation...”
Based on the reviewers comments we have now added the following sentences:
Changes in fatigue were positively associated with changes in the other cancer related symptoms as assessed by ESAS (Table 7)[Results, Page 9, para 3]; “The results of this study suggest that the changes in the fatigue scores were positively associated with the changes in the severity of other ESAS symptoms; these finding would strongly imply a causal relation between symptom load and fatigue.[discussion, Page 11, para 4]"

Need to clarify in the conclusion that fatigue is the most severe symptom rather than fatigue is the most commonly reported symptom as no percentages were given.
Based on the reviewers comment we have now revised the conclusion of the manuscript (Page 13) to clarify that fatigue is the most severe symptom rather than fatigue is most commonly reported symptom based on the data. “Our findings suggest that fatigue is the most severe symptom in patients with advanced cancer. Severity levels of pain, depression, appetite, nausea, drowsiness, well-being, and shortness of breath and the albumin level were predictive of the severity of fatigue at the time of the initial consultation, with pain and low appetite being the most significant predictors. Genitourinary cancer and low appetite at baseline were associated with successful improvement of fatigue.”

Clarify the explanation given for the “relation between GU cancer and decrease in fatigue. The authors mention androgen deprivation...”
Based on the comments of the reviewer we have now revised the discussion section of the manuscript (Page 11, para 3) to clarify the possible relation between GU cancer and decrease in fatigue: “In patients with prostate cancer, anorexia cachexia is less important contributor to fatigue. [31] The authors speculate that fatigue as a result of androgen deprivation in prostate cancer patients may be more amenable to palliative interventions such as exercise.[33,34]"

Reviewer 2
“...It might be said that some statistically significant association might be found if sufficient factors are looked at and this may explain findings which may or may not prove to be confirmed in future studies...”
Based on the reviewers comments we have now added a sentence in the discussion under limitation on page 12, para 2 that: “Some of the statistically significant associations in this study may be as a result of multiple analysis. Future prospective studies are needed to confirm these findings.”