PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of resilience with health-related quality of life and depression in Multiple Myeloma and its precursors – Results of a German cross-sectional study
AUTHORS	Maatouk, Imad; He, Susanne; Becker, Natalia; Hummel, Manuela; Hemmer, Stefan; Hillengass, Michaela; Goldschmidt, Hartmut; Hartmann, Mechthild; Schellberg, Dieter; Herzog, Wolfgang; Hillengass, Jens

VERSION 1 – REVIEW

REVIEWER	Anja Mehnert University Medical Center Leipzig, Germany
REVIEW RETURNED	25-Feb-2018

GENERAL COMMENTS	This study aims to determine the relationship between resilience, depression and quality of life in patients with Multiple Myeloma. Introduction: Page 4, the authors state that "the concept of resilience gets increasing attention in the field of cancer". Well, that is not entire the case. It has been well examined through the last 20, thirty years. In this respect, the introduction does not well address major research findings on resilience in cancer. The novelty and rationale for this study is not convincing except that resilience has not been much studied in patients with Multiple Myeloma. However, the authors need to explain the difference in patients with Multiple Myeloma compared to other cancer populations or its specificity. Also, a regression analyses has been done. I assume the authors have had a detailed research aim or hypotheses about it. Please report in more detail. Method: Please add eligibility criteria for the study. Did participants provide written informed consent? Please clarify. Why were laboratory test parameters such as calcium collected? Do you have any hypothesis including physical parameters associated with resilience? Measures: The references for the German validations of the measures used are missing. Please add. 312 consecutive patients were enrolled in this study out of how many eligible patients? Please provide response rate. Is there any information available about non-responders that could lead to estimations for a sample bias? Discussion: the concept of resilience needs to be described in the introduction, not the discussion. Please check your statement page 14 "Our results are in line with a small study of Schumacher et al. 17 that were the first who

	demonstrated a link between resilience and HRQOL in a rather small sample of 75 haematological patients after SCT. " There are so many trails out describing the association between resilience and quality of life. The authors might want to rethink the limitations of their study. They report no eligibility criteria, no responder-analyses, no hypotheses for their analyses and miss significant parts of the already existing and rather large body of research in this area. I don't think the conclusion makes sense. Why should we screen for resilience rather than for depression or any other kind of distress or QoL.

REVIEWER	Madelon Peters Maastricht University, the netherlands
REVIEW RETURNED	25-Mar-2018

GENERAL COMMENTS	The paper of Maatouk et al describes a cross sectional questionnaire study among MM patients on the association between resilience and quality of life and depression. A large sample of patients was included and various stages of the disease are represented. The major limitation, the cross-sectional nature of the study, is acknowledged. The data can nevertheless yield interesting insights in the role of resilience in coping with cancer. I have some comments and suggestions to improve the paper. The introduction could provide a stronger rational for the inclusion of MGUS and SMM participants. It is claimed that ".. in all phases of the disease trajectory (including premalignant stages) patients may experience physical and mental impairment." This is not further explained, the subsequent text cites evidence for lower HRQOL in MM only. In the discussion the burden of an elevated risk is mentioned. I can see that this will have an impact on mental state, but how and why physical QOL is affected in people who experience "by definition absence of symptoms" needs further explanation. Related to this issue, the regression analyses show that stage of disease is significantly related to MCS but not to PCS. PCS is significantly higher in patients in earlier stages of diagnosis. Can authors say anything about the scores in the premalignant group? How does this compare to a community sample for instance? After all, the SF-12 was chosen to enable comparison across studies and groups. It would also be interesting to include an interaction term (disease stage x resilience) in the regression analyses, to see whether the association between resilience and the three outcomes is the same for each group (i.e. moderator analysis). If disease stage does not matter, could it be that an association between resilience and QOL/depression is present in all people, i.e. independent of the presence of any disease? In other words, do all people benefit from resilience? There is no healthy control group, thus one can only speculate about this. See for instance Markovitz, Schrooten, Arntz & Peters, Psychooncology, 2015: Resilience as a predictor for emotional response to the diagnosis and surgery in breast cancer patients. The issue of specificity of the findings for (cancer) patients could be addressed in the discussion. The introduction should also contextualize the current study in prior research findings. For instance, it is noted: "…the concept of

	resilience gets increasing attention in the field of cancer." However, no studies and/or what these studies found are cited here. What follows is a definition of resilience and the mention that resilience might be learned. The latter would be more appropriate for the discussion (i.e. clinical implications). One would expect at least some references of other studies having demonstrated the importance of resilience in cancer patients. The discussion might benefit from a little more substance. For instance, under the heading "The concept of resilience and its significance in oncology" it does not really become clear in which way(s) resilience is defined. Initially it was viewed as a trait, but "later studies focused on a developmental perspective and an investigation of pediatric cancer survivors." What does this mean for how resilience should be viewed? And does the RS-13 measure resilience as a trait? Also its significance for cancer can be elaborated more. The section "comparison to other studies in the field" can be structured better. The relevance of the pathophysiological mechanism is not directly apparent. A paragraph on clinical implications could be added. Some other comments: What is the scoring range for PCS and MCS? Is the usual 0 – 100 scale used? If so, the patient group seems to score extremely low. This might need some mention. The cut-off points for PHQ-9 and RS-13 are not very clearly described. For PHQ-9 the same cut-off point (15) is mentioned twice. For the RS-13 the interpretation of scores 73-76 is missing. It would be more clear to not speak of cut-off points but just give the various ranges with their interpretation. One can also wonder whether it is necessary at all to work with cut-off points. In the regression analyses, resilience now has 3 levels, whereas in fact it is a continuous measure. Why not use it as such? Categorization of continuous variables leads to a loss of power and is not recommended unless there are very good reasons to do so. The same can be said for the depression score. Because prevalence of depression per se is not the target of this paper, one could easily use the continuous depression score as the dependent variable. Thus I would recommend, where possible, to use continuous scores in the regression analyses The reference category for disease stage is premalignant stage. In the statistical paragraph is says: MM or SMM. At points there is some needless repletion in the text, e.g. "Multiple regression analyses were conducted separately for the following dependent variables: MCS/PCS (as continuous variables) and severity of depression symptoms (none/mild/moderate/severe)." Or on page 9: "As mentioned above, our dependent (outcome) variable were MCS and PCS respectively." Bottom page 14: SCT is not defined.

VERSION 1 – AUTHOR RESPONSE

Dear Editor,
Enclosed please find the revision of the above manuscript. We would like to thank the reviewers for their thoughtful and constructive comments and the time spent on the evaluation of our manuscript. According to your suggestions, we rewrote the content together with the necessary editorial changes as per the comments of the reviewers.
Please see our detailed response to the reviewers' concerns below.

1. This study aims to determine the relationship between resilience, depression and quality of life in patients with Multiple Myeloma.
Introduction: Page 4, the authors state that "the concept of resilience gets increasing attention in the field of cancer". Well, that is not entire the case. It has been well examined through the last 20, thirty years. In this respect, the introduction does not well address major research findings on resilience in cancer. The novelty and rationale for this study is not convincing except that resilience has not been much studied in patients with Multiple Myeloma. However, the authors need to explain the difference in patients with Multiple Myeloma compared to other cancer populations or its specificity. Also, a regression analyses has been done. I assume the authors have had a detailed research aim or hypotheses about it. Please report in more detail.

Answer: We thank the reviewer for this comment indicating that we should have been clearer (and more thoroughly) on the mentioned points. We have added a paragraph regarding the large body of research on resilience in cancer. In addition, we describe the specific characteristics of multiple myeloma to underline the relevance of our study. Further, we have added a small paragraph with a detailed research aim and hypotheses:

Page 4-6: "Survivors of MM have to cope with numerous symptoms due to organ damage caused by the disease as well as with the psychosocial burden over years. Long-lasting effects due to the drugs toxicities may be apparent after its completion.4 The mentioned symptoms of the disease and side effects of its treatments lead to a deterioration of health-related quality of life (HRQOL). Due to the by definition absence of symptoms in MGUS and SMM, respectively, most patients do not need treatment right away but have to be monitored in an adequate manner. However, in all phases of the disease trajectory (including premalignant stages) patients may experience physical and mental impairment. 4 5 ... The self-perception and subjective assessment of one's own physical health-related quality of life could be impaired even in asymptomatic precursor states such as MGUS and SMM. Clinical observations show that older patients more often tend to name physical symptoms/limitations than mental difficulties. The awareness of the risk of developing a malignant disease could impair the perception of one's own physical quality of life. From a clinical perspective, this is a burden for many patients with premalignant stages of MM. However, there is no single published study that investigated HRQOL or psychological burden in patients with MGUS and SMM. … The concept of resilience has been well studied in recent decades in the field of cancer. In a recently published comprehensive review of resilience in adult cancer care the authors conclude to "define resilience in adult patients with cancer and survivors as a dynamic process of facing adversity related to the cancer experience."10 It is conceptualized as the ability to bounce back from highly adverse conditions like a serious health problem. Studies in patients with different cancer types (e.g. breast, lung, gastric cancer) suggest positive associations between resilience and HRQOL 11-14. and lower emotional distress, respectively 15 16. However, there is a paucity of research evaluating the possible relevance of resilience in patients with MM. Myeloma patients are affected by numerous symptoms that can affect many organs. The disease is still incurable today. In the preliminary stages (without treatment) the uncertainty represents a strong burden and after the possibly achieved remission (after treatment) there is a high risk of recurrence. 4 Furthermore, men are predominantly affected at a median age of 70 years. This group is known to have less access to psycho-oncological

interventions, often evaluated in younger patients with breast cancer.17 Therefore, the nature of protective factors such as resilience in MM and its precursors has to be elucidated.
The purpose of this study was therefore to examine associations between resilience, HRQOL and depressive symptoms in a large sample of adult patients with MM, SMM and MGUS.
The following research questions were addressed in detail:
Is there a significant relation between resilience and mental and physical HRQOL, respectively? Is there a significant relation between resilience and depression severity?
Further we wanted investigate possible differences in the associations between resilience and the various outcomes (HRQOL and depression, respectively) for the different stages of MM under consideration of its precursors. To the best of our knowledge, this is the first study to investigate the impact of resilience in the course of disease of MM."

2. Method: Please add eligibility criteria for the study. Did participants provide written informed consent? Please clarify. Why were laboratory test parameters such as calcium collected? Do you have any hypothesis including physical parameters associated with resilience?
Measures: The references for the German validations of the measures used are missing. Please add.

Answer: We agree with the reviewers comment and have detailed the eligibility criteria in the methods section. Written, informed consent was obtained from all participants. The laboratory parameters tested are part of the routine diagnostic work up of multiple myeloma with especially calcium being an important clinical factor for the definition of the stage of the disease. Possible relations between physical parameters and resilience were not part of the current analyses. We agree with the reviewer's comment regarding the references for German validations and have added them to the reference list accordingly.

Page 6/7 "During the aforementioned period, all patients who had a first presentation at the center with a diagnosis of MM, SMM and MGUS who had sufficient skills in reading and writing German were eligible for study participation. Patients who had submitted written informed consent were included. Exclusion criteria were as follows: cognitive impairment (i.e. not being able to follow the informed consent or other indications that the contents of the procedure cannot be followed) and serious psychiatric illnesses at the time of presentation. Severe psychiatric symptoms were defined as follows: requiring an immediate treatment such as acute suicidal tendencies, psychotic symptoms, dissociation or flash backs and severe addictive diseases. The questionnaires were to be completed at home and given to a staff member at the first appointment in the clinic. Written, informed consent was obtained from all participants. Participation was voluntary, and participants could withdraw at any time without any consequences. Ethical approval was obtained from the local ethics committee. Patients were not involved in the recruitment to and conduct of the study. Results will be disseminated to study participants through annual information events and contact with self-help groups. "

3. 312 consecutive patients were enrolled in this study out of how many eligible patients? Please provide response rate. Is there any information available about non-responders that could lead to estimations for a sample bias?

Answer: Thank you for mentioning this important point. From November 2014 to April 2016 all patients who had a first presentation at the center who had sufficient skills in reading and writing German and had submitted written informed consent were included. In determining the non-participants, we found that 16 of the initially included subjects had not signed the consent form even though they had completed the questionnaire. These had to be excluded from the current analyses for the revised paper. Further, one participant was listed repeatedly in the database and one participant had to be excluded due to a wrong diagnosis. After this final data cleansing, the result was a total

sample of 292 participants. The results did not differ from results of prior analyses. These 292 consecutive patients were enrolled in this study out of 578 eligible patients. We have added a paragraph at the beginning of the methods section and a figure with a flow chart accordingly.

Page 9/10: “Between November 2014 and April 2016, 292 out of 578 eligible Patients (response rate: 50.5%) were enrolled in the study (Figure 1)…
Non-responder Analyses
We analyzed differences in age, sex, and disease stage between study participants (n=292) and non-participants (n=286). No statistically significant differences were found with regard to age (participants: median=62.5 versus non-participants: median=62.9; p=0.77), sex (participants: female n=119 (40.8%); male n=173 (59.2%) versus non-participants: female n=114 (39.9%); male n=172 (60.1%); p=0.89) and disease stage (participants: MGUS, SMM n=88 (30.1%); new diagnosis of MM n=98 (33.6%); treated MM n=106 (36.3%) versus non-participants: MGUS, SMM n=95 (33.2%); new diagnosis of MM n=73 (25.5%); treated MM n=118 (41.3%); p=0.11)”

4. Discussion: the concept of resilience needs to be described in the introduction, not the discussion.

Answer: We agree with this comment. In the revised manuscript, we introduce the concept of resilience and mention important prior studies regarding resilience in cancer patients in the introduction section.

5. Please check your statement page 14 "Our results are in line with a small study of Schumacher et al. 17 that were the first who demonstrated a link between resilience and HRQOL in a rather small sample of 75 haematological patients after SCT. " There are so many trails out describing the association between resilience and quality of life.

Answer: We apologize for being imprecise and misleading here. We wanted to point out that there is only one single study on resilience that includes myeloma patients. The study of Schumacher et al. included a small heterogeneous sample of 75 hematological patients (leukemia, lymphoma, myeloma, aplastic anemia). Unfortunately, the number of individual entities was not specified in more detail. Of course there are numerous studies that deal with resilience and quality of life. However, we need to discuss the already existing body of research in this area. In the revised manuscript we have added a paragraph regarding prior research findings accordingly. Nevertheless, we have tried to keep it short, following the author guidelines, which recommend a word limitation of 4000 words for better readability.

6. The authors might want to rethink the limitations of their study. They report no eligibility criteria, no responder-analyses, no hypotheses for their analyses and miss significant parts of the already existing and rather large body of research in this area.
I don't think the conclusion makes sense. Why should we screen for resilience rather than for depression or any other kind of distress or QoL.

Answer: We agree with the reviewer’s comment. We have added eligibility criteria, responder-analyses, hypotheses and existing studies. Further, we have modified our conclusion:
“In conclusion, resilience may be a protective factor in the disease trajectory of MM and its precursors. As a next step, future research should focus on longitudinal assessments at various time points to elucidate the role of resilience in one of the most frequent hematological malignancies.“

Reviewer: 2
Reviewer Name: madelon peters
Institution and Country: Maastricht University, the netherlands

Competing Interests: none declared

The paper of Maatouk et al describes a cross sectional questionnaire study among MM patients on the association between resilience and quality of life and depression. A large sample of patients was included and various stages of the disease are represented. The major limitation, the cross-sectional nature of the study, is acknowledged. The data can nevertheless yield interesting insights in the role of resilience in coping with cancer.

I have some comments and suggestions to improve the paper.

1. The introduction could provide a stronger rational for the inclusion of MGUS and SMM participants. It is claimed that ".. in all phases of the disease trajectory (including premalignant stages) patients may experience physical and mental impairment." This is not further explained, the subsequent text cites evidence for lower HRQOL in MM only. In the discussion the burden of an elevated risk is mentioned. I can see that this will have an impact on mental state, but how and why physical QOL is affected in people who experience "by definition absence of symptoms" needs further explanation.

Answer: Thank you for this comment. It is true that mental rather than physical limitations are to be expected in the preliminary stages (MGUS, SMM). However, the self-perception and subjective assessment of one's own physical health-related quality of life could be impaired. This finding is in accordance with our clinical observations. Older patients more often name physical symptoms and limitations than mental difficulties. The possibility of suffering from a serious disease is a burden for many patients. There is no literature on mental stress or HRQOL in the pre-stages of MM. We have added a sentence in the introduction section and paragraph in the discussion section accordingly.

Page 4/5: "However, in all phases of the disease trajectory (including premalignant stages) patients may experience physical and mental impairment. 4 5 HRQOL "refers to the physical, psychological, and social domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations, and perceptions"6. The self-perception and subjective assessment of one's own physical health-related quality of life could be impaired even in asymptomatic precursor states such as MGUS and SMM. Clinical observations show that older patients more often tend to name physical symptoms/limitations than mental difficulties. The awareness of the risk of developing a malignant disease could impair the perception of one's own physical quality of life. From a clinical perspective, this is a burden for many patients with premalignant stages of MM. However, there is no single published study that investigated HRQOL or psychological burden in patients with MGUS and SMM."

Page 20: "At the age of 70 years and older the prevalence of MGUS is about 5%. The vast majority of patients will not develop MM, but will suffer from the psychological consequences of elevated risk. They have to be monitored in an adequate manner. Patients with SMM are monitored every 3 months and a considerable part of these patients will be stressed by regularly advised diagnostic visits.2 25 The regression analyses show that the stage of the disease was significantly related to PCS but not to MCS. This appears to be plausible because physical problems increase in later phases of the disease, while mental burden seems to be high in all phases. Further studies within a larger sample are planned to investigate the differences with regard to HRQOL and psychological burden between the individual stages of the disease in more detail and under consideration of comparisons with HRQOL scores of a community sample. "

2. Related to this issue, the regression analyses show that stage of disease is significantly related to MCS but not to PCS. PCS is significantly higher in patients in earlier stages of diagnosis. Can authors say anything about the scores in the premalignant group? How does this compare to a community

sample for instance? After all, the SF-12 was chosen to enable comparison across studies and groups.

Answer: This is an important point. The regression analyses show that the stage of disease is significantly related to PCS but not to MCS. Indeed, PCS is significantly higher in patients in earlier stages of diagnosis. However, the investigation of different outcomes (HRQOL and psychological burden) in the various stages of MM and a comparison with the respective community sample will be the focus of another (future) work with a much larger sample. Since this was not the focus of the current study, we did not want to anticipate further results here. However, it appears that the mean PCS score of the premalignant group is comparable to the representative community sample whereas the mean MCS score of the premalignant group is about 5 points lower than in the German normative population. This point needs further attention.

3. It would also be interesting to include an interaction term (disease stage x resilience) in the regression analyses, to see whether the association between resilience and the three outcomes is the same for each group (i.e. moderator analysis).

Answer: We appreciate this advice and have therefore carried out additional analyses. For better readability of the manuscript (according to the authors instructions) we mention the results of our additional analyses at the end of the results section and discuss them in the discussion section. Further we have added the tables of additional analyses as "Supplementary Content".

Page 17:
“Additional analyses with continuous scores and interaction terms
The correlations of the results in the sensitivity analyses with continuous scores were consistent with the results shown above. Moderator analyses revealed that stage of Myeloma moderates the association between resilience and HRQOL and depression respectively. The association between resilience and mental quality of life (MCS) was stronger in patients at an earlier stage (before treatment). With regard to the physical sum score (PCS) resilience had a stronger association at earlier stage (before treatment). Further, the inverse association of resilience and depression was stronger in patients at an earlier stage (before treatment). Results of additional analyses are shown in table 5 to 7 in a supplementary data file.

4. If disease stage does not matter, could it be that an association between resilience and QOL/depression is present in all people, i.e. independent of the presence of any disease? In other words, do all people benefit from resilience? There is no healthy control group, thus one can only speculate about this. See for instance Markovitz, Schrooten, Arntz & Peters, Psychooncology, 2015: Resilience as a predictor for emotional response to the diagnosis and surgery in breast cancer patients. The issue of specificity of the findings for (cancer) patients could be addressed in the discussion.

Answer: Thank you for pointing this out. We have now taken this aspect into account in our discussion section. (Page 18/19)

5. The introduction should also contextualize the current study in prior research findings. For instance, it is noted: “…the concept of resilience gets increasing attention in the field of cancer.” However, no studies and/or what these studies found are cited here. What follows is a definition of resilience and the mention that resilience might be learned. The latter would be more appropriate for the discussion (i.e. clinical implications). One would expect at least some references of other studies having demonstrated the importance of resilience in cancer patients.

Answer: We agree with this comment. As stated above (regarding the comments of the first reviewer) we need to discuss the already existing body of research in this area. In the revised manuscript we have added a paragraph regarding prior research findings accordingly. (Page 4-6)

6. The discussion might benefit from a little more substance. For instance, under the heading “The concept of resilience and its significance in oncology” it does not really become clear in which way(s) resilience is defined. Initially it was viewed as a trait, but “later studies focused on a developmental perspective and an investigation of pediatric cancer survivors.” What does this mean for how resilience should be viewed? And does the RS-13 measure resilience as a trait? Also its significance for cancer can be elaborated more.
The section “comparison to other studies in the field” can be structured better. The relevance of the pathophysiological mechanism is not directly apparent. A paragraph on clinical implications could be added.

Answer: We agree with this comment. In the revised manuscript we have deleted the section on pathophysiological relationships and focused on the existing literature and possible clinical implications. (Page 17-21)

Some other comments:

7. What is the scoring range for PCS and MCS? Is the usual 0 – 100 scale used? If so, the patient group seems to score extremely low. This might need some mention.

Answer: Yes. The usual 0-100 scale is used. As stated above, the investigation of different outcomes (HRQOL and psychological burden) in the various stages of MM and a comparison with the respective community sample will be the focus of another (future) work with a much larger sample. Since this was not the focus of the current study, we did not want to anticipate further results here. As stated in the introduction section, MM has a strong negative impact on several aspects HRQOL, which explains the low ratings.

8. The cut-off points for PHQ-9 and RS-13 are not very clearly described. For PHQ-9 the same cut-off point (15) is mentioned twice. For the RS-13 the interpretation of scores 73-76 is missing. It would be more clear to not speak of cut-off points but just give the various ranges with their interpretation.

Answer: Thank you for this comment. From a clinical point of view cut-offs are important. For better readability we have modified the respective paragraph.
Page 7/8: “The total score of all items of the PHQ-9 ranges between 0 and 27 points. A range from 0-4 points suggests no clinically significant symptoms, 5-9 points indicate mild depressive symptoms, 10-14 points refer to moderate symptoms and 15–27 points suggest the existence of severe depressive symptoms. Resilience was measured by the short form of the Resilience scale (RS-13), a well validated questionnaire derived from the original scale of Wagnild and Young.22 23 The total score of all items ranges between 13 and 91 points. Respective ranges were used to categorize the `level of resilience`. A range from 13-65 points refer to a low level of resilience, a range from 67-72 points suggest a moderate level of resilience and 77-91 points indicate a high level of resilience.”

9. One can also wonder whether it is necessary at all to work with cut-off points. In the regression analyses, resilience now has 3 levels, whereas in fact it is a continuous measure. Why not use it as such? Categorization of continuous variables leads to a loss of power and is not recommended unless there are very good reasons to do so. The same can be said for the depression score. Because prevalence of depression per se is not the target of this paper, one could easily use the

continuous depression score as the dependent variable. Thus I would recommend, where possible, to use continuous scores in the regression analyses.

Answer: We basically agree with this comment, but these cut-offs are often taken into account in everyday clinical practice because they provide orientation for the clinician. However, for sensitivity analyses we performed additional analyses with continuous scores. For better readability we mention the results of those sensitivity analyses at the end of the results section. Further we have added the results as "Supplementary Content".

10. The reference category for disease stage is premalignant stage. In the statistical paragraph is says: MM or SMM.

Answer: Thank you very much. This is absolutely correct. MGUS and SMM are precursors (premalignant stages). We have corrected our mistake. (Page 8)

11. At points there is some needless repletion in the text, e.g. “Multiple regression analyses were conducted
separately for the following dependent variables: MCS/PCS (as continuous variables) and severity of depression symptoms (none/mild/moderate/severe).” Or on page 9: “As mentioned above, our dependent (outcome) variable were MCS and PCS respectively.”

Answer: Thank you for this comment. The wording has been reduced accordingly.

12. Bottom page 14: SCT is not defined.

Answer: A definition has been added.
Page 19:” stem cell transplantation (SCT).”

VERSION 2 – REVIEW

REVIEWER	Madelon Peters Maastricht University, the Netherlands
REVIEW RETURNED	14-May-2018

GENERAL COMMENTS	Thank you for giving me the opportunity to re-review the paper by Maatouk et al. The authors have taken all the comments of the reviewers in account and modified the paper accordingly. Overall, the paper has benefited from these modification. I nevertheless have several remaining concerns that authors may want to take into account. 1. There are a few redundancies in the introduction and method section. In the introduction it is mentioned at 2 places that MM may lead to organ damage and psychological burden. In the method section, it is mentioned twice that data collection took place from Nov 2014 to April 2016. 2. Some additions impact on the logical flow of the text. For instance, in the introduction the added sentence comments that it is important to gain more knowledge on protective factors. In the next sentence it is noted that complementary to the study of impairments, resilience should be studied. The “However” in this sentence is no longer appropriate because the new sentence already introduced

	the protective factors. 3. I suggest deleting “in detail” after “the following questions were addressed. 4. I do not understand the meaning of “of its precursors “ in the sentence “Further we wanted investigate possible differences in the associations between resilience and the various outcomes (HRQOL and depression, respectively) for the different stages of MM under consideration of its precursors”. 5. There are still some scores missing in the cut-offs for RS-13. To what category do patients belong if they have a score of 66, or 73 – 76? 6. In the non-responder analysis, it would be sufficient to only mention the % of men (or women) instead of both sexes. 7. There is a heading “non-responder analysis” and one for the “additional analyses”, but no heading for the core results. As it is, they would now belong to the section non-responder analysis. 8. I would suggest removing the sensitivity analyses from the moderator paragraph. The moderator analyses are directed at one of the research aims, whereas the sensitivity analysis is merely a check on the validity of the results. This could be placed in the previous section. Also, this section might be more appropriately named “moderator analyses”, because they are not post hoc analyses (they address – albeit novel – research aim), as might be suggested by the title. 9. It is somewhat confusing to read that analyses with the continuous scores were “consistent” with the categorical analyses. At least concerning resilience. What does consistent mean in this case? Only the contrast high vs low resilience reached significance re its association with the three outcomes. The contrast moderate vs low significance did not. This could either point at a non-linear association between resilience and HRQOL/depression, or merely reflects the fact that moderate resilience (which represents quite a small range of scores) differs less from low resilience (with a very broad range of scores) than the other contrast. It would therefore be interesting to know whether regression analyses with the continuous resilience variable point towards a linear association with the various outcomes or a quadratic term would be more appropriate. 10. I have doubt whether the results of the moderator analyses are interpreted correctly. While the new diagnosis – premalignant contrast was significant for MCS and depression, the treated MM – premalignant contrast reached significance for PCS. It seems as if treated patients have a negative association between resilience and PCS. 11. In the discussion, the added text after “what could be the reason for this” does not follow logically after this question. One expects an explanation of difference in strength of association between the groups. However, the first part relates to the definition of resilience and does not seem relevant in this particular place. Nor the “limitation” of not having a control group. The later could possibly be moved to the limitation section. Or to another section in the discussion. Only the vary last part of this new section actually

	addresses the differences in strength of association between the groups (note that this should also be made consistent with the results if indeed these are interpreted incorrectly). 12. The whole discussion could be structured somewhat better.

VERSION 2 – AUTHOR RESPONSE

Reviewer's Comments to Author:

Thank you for giving me the opportunity to re-review the paper by Maatouk et al. The authors have taken all the comments of the reviewers in account and modified the paper accordingly. Overall, the paper has benefited from these modification.

I nevertheless have several remaining concerns that authors may want to take into account.

1. There are a few redundancies in the introduction and method section. In the introduction it is mentioned at 2 places that MM may lead to organ damage and psychological burden. In the method section, it is mentioned twice that data collection took place from Nov 2014 to April 2016.

Answer: We agree with the reviewer's comment and have removed the repetitions accordingly.

2. Some additions impact on the logical flow of the text. For instance, in the introduction the added sentence comments that it is important to gain more knowledge on protective factors. In the next sentence it is noted that complementary to the study of impairments, resilience should be studied. The "However" in this sentence is no longer appropriate because the new sentence already introduced the protective factors.

Answer: This is correct. The text has been revised accordingly.

3. I suggest deleting "in detail" after "the following questions were addressed.

Answer: We agree with this suggestion and have deleted the term accordingly

4. I do not understand the meaning of "of its precursors "in the sentence "Further we wanted investigate possible differences in the associations between resilience and the various outcomes (HRQOL and depression, respectively) for the different stages of MM under consideration of its precursors".

Answer: We apologize for being misleading here. We have shortened the sentence accordingly.

5. There are still some scores missing in the cut-offs for RS-13. To what category do patients belong if they have a score of 66, or 73 – 76?

Answer: This is correct. We want to apologize for making a mistake here and thank the reviewer for his careful attention. In the revised manuscript we have inserted the correct values with respective categorization according to the German validation study (Citation No. 22 of Leppert et al.):

"A range from 13-66 points refers to a low level of resilience, a range from 67-72 points suggests a moderate level of resilience and 73-91 points indicate a high level of resilience."

6. In the non-responder analysis, it would be sufficient to only mention the % of men (or women)

instead of both sexes.

Answer: We have modified the text accordingly:

“

7. There is a heading “non-responder analysis” and one for the “additional analyses”, but no heading for the core results. As it is, they would now belong to the section non-responder analysis.

Answer: This is absolutely correct. We have modified the headings accordingly.

8. I would suggest removing the sensitivity analyses from the moderator paragraph. The moderator analyses are directed at one of the research aims, whereas the sensitivity analysis is merely a check on the validity of the results. This could be placed in the previous section. Also, this section might be more appropriately named “moderator analyses”, because they are not post hoc analyses (they address – albeit novel – research aim), as might be suggested by the title.

Answer: We agree with this comment. As stated in our prior response we have restructured the headings of our results section accordingly.

9. It is somewhat confusing to read that analyses with the continuous scores were “consistent” with the categorical analyses. At least concerning resilience. What does consistent mean in this case? Only the contrast high vs low resilience reached significance re its association with the three outcomes. The contrast moderate vs low significance did not. This could either point at a non-linear association between resilience and HRQOL/depression, or merely reflects the fact that moderate resilience (which represents quite a small range of scores) differs less from low resilience (with a very broad range of scores) than the other contrast. It would therefore be interesting to know whether regression analyses with the continuous resilience variable point towards a linear association with the various outcomes or a quadratic term would be more appropriate.

Answer: We agree with the evaluation that the current description can be rather confusing for the reader. It is correct that the contrast moderate vs low resilience did not reach significance. This reflects the fact that moderate resilience (which represents quite a small range of scores) differs less from low resilience (with a very broad range of scores) than the other contrast. Linear regression analyses with the continuous resilience variable showed a significant linear association with the respective outcomes (of PCS/MCS and continuous PHQ-9 score). Graphical inspection of the data did not indicate quadratic or other non-linear relationships. We have modified the section accordingly:

“Linear regression analyses with the continuous resilience variable showed a significant linear association with the respective outcomes of PCS/MCS (positive association) and continuous PHQ-9 score (negative association). Graphical inspection of the data did not indicate quadratic or other non-linear relationships. The results are shown in a supplementary data file with supplementary tables 1-3.”

10. I have doubt whether the results of the moderator analyses are interpreted correctly. While the new diagnosis – premalignant contrast was significant for MCS and depression, the treated MM – premalignant contrast reached significance for PCS. It seems as if treated patients have a negative association between resilience and PCS.

Answer: We thank the reviewer for this comment indicating that we should have been clearer with the description of the results of the moderator analyses. With regard to MCS and PHQ-9 scores resilience for patients with new diagnosis has the strongest influence. With regard to PCS12 there is a

significant (main) effect of resilience (b=0.29), while for PCS12 in the “after therapy”-group it is very small or not present. The resilience – after therapy interaction effect has a negative sign (for PCS12), since in the after therapy group the effect of resilience on PCS12 is significantly lower (however, still positive: 0.29 minus 0.23) than in the MGUS, SMM group. This means that resilience has almost no protective effect on the physical quality of life in patients already treated. We have modified the paragraph of the moderator analyses accordingly:

“Moderator analyses revealed that stage of Myeloma moderates the association between resilience and HRQOL and depression respectively. The association between resilience and mental quality of life (MCS) was significantly stronger in patients with a new diagnosis. The association between resilience and physical quality of life (PCS) was significantly weaker in patients with treated MM. With regard to PCS in the “treated MM”-group the remaining effect of resilience is very small. Further, the inverse association of resilience and depression was significantly stronger in patients with a new diagnosis of MM. Results of moderator analyses are shown in a supplementary data file with supplementary tables 1-3.”

11. In the discussion, the added text after “what could be the reason for this” does not follow logically after this question. One expects an explanation of difference in strength of association between the groups. However, the first part relates to the definition of resilience and does not seem relevant in this particular place. Nor the “limitation” of not having a control group. The later could possibly be moved to the limitation section. Or to another section in the discussion. Only the vary last part of this new section actually addresses the differences in strength of association between the groups (note that this should also be made consistent with the results if indeed these are interpreted incorrectly).

Answer: We agree with this comment. In the first revision of the manuscript, we introduce the concept of resilience and mention important prior studies regarding resilience in cancer patients in the introduction section. In the discussion of the current version we have shortened the “definition of resilience-paragraph” and we have modified the structure of the whole discussion.
The differences between groups are addressed as follows:

“The regression analyses show that the stage of the disease was significantly related to PCS but not to MCS. This appears to be plausible because physical problems increase in later phases of the disease, while mental burden seems to be high in all phases.
Moderator analyses reveal that resilience has a stronger link to MCS and depression in patients with a new diagnosis and a weaker association to PCS in patients with treated MM.
With regard to MM one can imagine that patients at an early stage (before the start of therapy) are particularly challenged to anticipate coping with the disease and the upcoming therapy. In our sample, resilience could have a stronger protective effect on mental aspects of HRQOL and depression in early (untreated) stages, than at a later point in time, if the burden by the demanding therapy such as high dose chemotherapy with autologous stem cell transplantation (ASCT) determines the state of perceived mental health. Physical aspects of quality of life (PCS) hardly seem to be influenced by resilience in treated patients, since other factors (e.g. symptoms of illness, side effects of therapy) probably play an overwhelming role. “

12. The whole discussion could be structured somewhat better.
We agree with this comment. We have modified the structure of the whole discussion.

We trust that these changes meet with your approval. Should you require further adjustments, please do not hesitate to get in touch with us. Thank you very much for your time. We are looking forward to hearing from you.

VERSION 3 – REVIEW

REVIEWER	Madelon Peters Maastricht University
REVIEW RETURNED	23-Jun-2018

GENERAL COMMENTS	The authors have adequately revised the manuscript.I have no further comments