

PEER REVIEW HISTORY

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ARTICLE DETAILS

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| TITLE (PROVISIONAL) | Parallel and serial mediation analysis between Pain, Anxiety, Depression, Fatigue and Nausea, Vomiting and Retching within a randomised controlled trial in breast and prostate cancer patients |
| AUTHORS | Charalambous, Andreas; Giannakopoulou, Margarita; Bozas, Evaggelos; Paikousis, Lefkios |

VERSION 1 – REVIEW

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| REVIEWER | Jiyeon Lee Chungnam National University, South Korea |
| REVIEW RETURNED | 17-Oct-2018 |

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| GENERAL COMMENTS | <p>Authors explored interrelations among symptoms which form symptom cluster, and mediation effect of symptoms on HRQOL, as well as moderation effect of sex on the relationships of symptoms and HRQOL. Serial mediation analysis further explored the relationship among symptoms considering the order of the mediation. Authors are recommended to consider following comments for revision.</p> <ol style="list-style-type: none">1. Design of the study: Authors needs to be clear that this is not a report about an RCT, but a secondary data analysis from the RCT.2. Methods: Measurements and Statistical Analysis are needs to be included. Unclear whether authors utilized Global QOL (single item score or two item general health/global QOL score) for the analysis?3. Results: Providing summarized sample characteristics (including disease characteristics) would be helpful in understanding the result of the study. <p>Authors utilized correlation analysis to identify symptom clusters. Symptom clusters are often identified utilizing factor analysis, cluster analysis, or latent class analysis. High correlation between symptoms is suggestive of symptom clusters but less often utilized technique. However, previous stuides about symptom clusters suggested the 4 symptoms as forming a symptom cluster, thus, authors needs to add references supportive of the symptom cluster membership.</p> <p>The direction of influence needs to be carefully interpreted. Current study identified significant relationship between pain and HRQOL which is mediated by anxiety, fatigue, and depression (no</p> |
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| | <p>indirect mediation of depression); which is in concordance of previous studies. However, authors discussed (suggested) that intervening anxiety, fatigue could ameliorate pain as well as HRQOL. Because authors investigated how anxiety and fatigue can mediate the influence of pain on HRQOL, the result still supported the notion that pain needs to be targeted first.</p> <p>Because all female patients were breast cancer patients and all male patients were prostate cancer patients, whether the moderating effect is from sex or cancer diagnosis is unclear. This needs to be discussed further.</p> <p>4. Funding: Please provide name of the funding (and number if available).</p> |
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| REVIEWER | Lei Zhu Shaanxi Normal University |
| REVIEW RETURNED | 17-Oct-2018 |

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| GENERAL COMMENTS | <p>This paper would be of interest to researchers and clinicians in psycho-oncology field. It is generally well-written, but needs substantial revision.</p> <p>1. The introduction The authors did not have separate paragraphs in the Introduction section, which has made the structure unclear. The authors should re-organize the introduction. Especially, the authors should provide evidence showing why examining the mediational models presented in the Results. What is the rationale behind these models? What are the specific hypothesis regarding these mediational models?</p> <p>2. Methods For each of the measures used, the authors should provide more detailed information, for example, answer category, total score, validity and reliability.</p> <p>3. Results Moderated mediation model: why the author was interested in examining the moderating role of gender? Again, the authors should have very clear rationale behind all the mediation models here presented in the Results.</p> <p>4. Discussion The authors stated that symptoms of pain, fatigue, anxiety and depression formed a common symptom cluster in both breast and prostate cancer patients. However, this has been consistently found in previous empirical studies. So, what is the added value of the findings of this paper?</p> |
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Jiyeon Lee

Institution and Country: Chungnam National University, South Korea

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Authors explored interrelations among symptoms which form symptom cluster, and mediation effect of symptoms on HRQOL, as well as moderation effect of sex on the relationships of symptoms and HRQOL.

Serial mediation analysis further explored the relationship among symptoms considering the order of the mediation.

Authors are recommended to consider following comments for revision.

1. Design of the study: Authors needs to be clear that this is not a report about an RCT, but a secondary data analysis from the RCT. → This point was further clarified in the abstract of the manuscript where the first sentence was revised as follows “This paper presents a secondary analysis of the data from a randomised control trial designed to test the effectiveness [...]”

Also in the Methods section the first sentence was revised to read as “The data for the purpose of this paper came from a Randomised Control Trial (NCT01275872) designed to test the effectiveness of [...]”

2. Methods: Measurements and Statistical Analysis are needs to be included. → The measurements were already included in the previous version. However, we have now used a sub-heading for measurements to make this more explicit. → a sub-heading was also used in the previous version for statistical analyses.

Unclear whether authors utilized Global QOL (single item score or two item general health/global QOL score) for the analysis? → We have utilized the two item general health/global QOL score

3. Results:

Providing summarized sample characteristics (including disease characteristics) would be helpful in understanding the result of the study. → A brief presentation of the sample characteristics has now been included in the manuscript. The following paragraph has been added in the text. “The sample consisted of 104 male (52 in the intervention group and 52 in the control group) and 104 female (52 in the intervention group and 52 in the control group) patients diagnosed with prostate and breast cancer. Eighty-six of the prostate cancer patients were diagnosed with stage T3a, Gleason score 8, and the remaining 18 with stage T3b, Gleason score 9. Patients with breast cancer were all diagnosed with clinical stage T3N1M0. Most of the participants belong to the 41-50 and the 51-60 age groups (38.9% and 26.4% respectively). Prostate cancer patients were treated either with a combination of androgen deprivation therapy (ADT) and adjuvant chemotherapy or with a combination of androgen deprivation therapy (ADT) and radiation (65.3% and 19.2% respectively).”

Authors utilized correlation analysis to identify symptom clusters.

Symptom clusters are often identified utilizing factor analysis, cluster analysis, or latent class analysis. High correlation between symptoms is suggestive of symptom clusters but less often utilized technique. However, previous studies about symptom clusters suggested the 4 symptoms as forming a symptom cluster, thus, authors needs to add references supportive of the symptom cluster membership. → In the discussion section, 2 references were added to support the symptom cluster membership. These references were:

So WK, Marsh G, Ling WM, Leung FY, Lo JC, Yeung M, Li GK. The symptom cluster of fatigue, pain, anxiety, and depression and the effect on the quality of life of women receiving treatment for breast cancer: a multicenter study. *Oncol Nurs Forum*. 2009 Jul;36(4):E205-14. doi: 10.1188/09.ONF.E205-E214.

Dirksen SR, Belyea MJ, Wong W, Epstein DR. Transitions in Symptom Cluster Subgroups Among Men Undergoing Prostate Cancer Radiation Therapy. *Cancer Nurs*. 2016;39(1):3-11.

The direction of influence needs to be carefully interpreted.

Current study identified significant relationship between pain and HRQOL which is mediated by anxiety, fatigue, and depression (no indirect mediation of depression); which is in concordance of previous studies.

However, authors discussed (suggested) that intervening anxiety, fatigue could ameliorate pain as well as HRQOL. Because authors investigated how anxiety and fatigue can mediate the influence of pain on HRQOL, the result still supported the notion that pain needs to be targeted first. → This was made clear in the paper's discussion by adding the following sentence "The results demonstrated the mediating effect of these symptoms on pain and HRQoL, however at the same time the results supported the notion that "pain" needs to be targeted first."

Because all female patients were breast cancer patients and all male patients were prostate cancer patients, whether the moderating effect is from sex or cancer diagnosis is unclear. This needs to be discussed further. → The authors have now included in the paper the main sample characteristics that demonstrate that the two patient groups were homogenous in terms of their cancer diagnosis. The moderating effects demonstrated by the results, derive from the cancer diagnosis (i.e. clinical characteristics and manifestations), as these differ between breast cancer patients and prostate cancer patients. Therefore through the analyses we wanted to examine the hypothesis that the mediation role of anxiety, depression and fatigue will differ between the breast cancer and prostate cancer diagnoses. Appropriate adjustments have been made throughout the paper to explicitly demonstrate this. The section "Moderated mediation model – Cancer diagnosis moderation" has been specifically revised to accommodate these changes. Finally, in the introduction the following sentence was added "Furthermore, the study hypothesises that the mediation role of anxiety, depression and fatigue will differ between the breast cancer and prostate cancer diagnoses."

4. Funding: Please provide name of the funding (and number if available). → The Cyprus University of Technology funded the study and it is included in the funding statement.

Reviewer: 2

Reviewer Name: Lei Zhu

Institution and Country: Shaanxi Normal University

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This paper would be of interest to researchers and clinicians in psycho-oncology field. It is generally well-written, but needs substantial revision.

1. The introduction

The authors did not have separate paragraphs in the Introduction section, which has made the structure unclear. The authors should re-organize the introduction. → This has been re-organised in separated paragraphs as recommended and this section has been revised to improve its flow.

Especially, the authors should provide evidence showing why examining the mediational models presented in the Results. What is the rational behind these models? → The following sentence has been added in the introduction to clarify this: "Therefore the rationale for examining these symptom clusters within the mediational models is to explicate whether these symptoms can have an alternative way of interaction other than the one suggested in a linear way. What is further lacking in the current research is the role of other possible mediators such as cancer diagnoses which is also explored within this study." Furthermore, the following sentences were revised to also make this explicit "When interventions are directed to ameliorate a particular symptom within a cluster, other symptoms within the cluster may be relieved. However this evidence is not available to the best of our knowledge in the suggested mediational models available in the literature"

What are the specific hypothesis regarding these mediational models? → The following sentence (i.e. hypothesis) was added "This study hypothesises that in the mediational models to be tested within this cluster of symptoms, fatigue, anxiety and depression will be identified as mediating factors in the pain-HRQoL linkage."

2. Methods

For each of the measures used, the authors should provide more detailed information, for example, answer category, total score, validity and reliability. → The requested details have been provided for each of the measures used in the study along with corresponding references.

3. Results

Moderated mediation model: why the author was interested in examining the moderating role of gender? Again, the authors should have very clear rational behind all the mediation models here presented in the Results. → As with the previous reviewer's comment, we have clarified (at point 3) that the moderating role of the cancer diagnosis was examined through the analyses. The following sentence was added in the manuscript to highlight this: "The moderating effects demonstrated by the results, derive from the cancer diagnosis (i.e. clinical characteristics and manifestations), as these differ between breast cancer patients and prostate cancer patients. Therefore through the analyses we wanted to examine the hypothesis that the mediation role of anxiety, depression and fatigue will differ between the breast cancer and prostate cancer diagnoses. Appropriate adjustments have been made throughout the paper to explicitly demonstrate this. The section "Moderated mediation model – Cancer diagnosis moderation" has been specifically revised to accommodate these changes." (Taken

from point 3 – reviewer 1). Furthermore, in the “statistical analysis” section the following sentence was added/revised as follows: “The second model is a moderated mediation model where the indirect effects of the mediating factors are explored on each cancer diagnosis (conditional indirect effects).” Finally, in the introduction the following sentence was added “Furthermore, the study hypothesises that the mediation role of anxiety, depression and fatigue will differ between the breast cancer and prostate cancer diagnoses.”

4. Discussion

The authors stated that symptoms of pain, fatigue, anxiety and depression formed a common symptom cluster in both breast and prostate cancer patients. However, this has been consistently found in previous empirical studies. So, what is the added value of the findings of this paper? → As stated in the aim of this study the focus was to “*provide evidence on the co-occurrence and interrelations between symptoms occurring as part of a cluster in two groups of patients diagnosed with breast and prostate cancer.*” According to the study’s aim, the results provided the evidence on the co-occurrence of the identified symptoms in a common cluster with the exception of N&V. Previous studies have provided evidence on the presence of the symptoms in different clusters, therefore our findings contribute to the existing knowledge on this topic. The study also contributed through its findings the evidence on the presence of this common cluster across two cancer patient groups (i.e. breast and prostate).

The first paragraph of the discussion was revised to reflect the above as follows: “The aim of this study was to explore the co-occurrence and interrelations between symptoms that were reported by two cancer patient groups and HRQoL. With previous findings showing that these symptoms can be present in different clusters in these groups of patients [30,31], we specifically aimed to demonstrate that pain, depression, fatigue, nausea, vomiting and retching and anxiety can form a common symptom cluster over the course of breast cancer and prostate cancer treatment. Findings showed that with the exception of nausea, vomiting and retching, the symptoms of pain, fatigue, anxiety and depression formed a common symptom cluster in both breast and prostate cancer patients.”

The second paragraph of the “discussion” section has presented the evidence to support the ways that the symptoms consisting of the cluster correlate, demonstrating the possible mediating effects. The 4th paragraph of the discussion, describes the clinical implications of the findings.

VERSION 2 – REVIEW

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| REVIEWER | Jiyeon Lee Chungnam National University |
| REVIEW RETURNED | 01-Nov-2018 |
| GENERAL COMMENTS | Authors revised the manuscript reflecting reviewer comments. |
| REVIEWER | Dr. Lei Zhu School of Psychology, Shaanxi Normal University, Xi'an, China |
| REVIEW RETURNED | 23-Nov-2018 |
| GENERAL COMMENTS | The authors have addressed my concerns. |