Author’s response to reviews

Title: Mediating effects of shoulder-arm exercise on the postoperative severity of symptoms and quality of life of women with breast cancer

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Version: 1 Date: 23 Apr 2020

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Manuscript ID: BMWH-D-20-00136

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April 6, 2020

Dear reviewers and editors,

Thank you for your thoughtful and insightful comments about our article. We revised the manuscript to reflect the reviewers’ and your suggestions. The revised manuscript is attached (revisions are in red type), and the revisions are summarized below:

Reviewer 1

Reviewer comments:
One of the problems with this study is that it does not state the type of surgery the women had. Specifically, it does not say break up the women into categories—whether women had mastectomies vs BCT.

Authors response and revisions:
We state that “Eighty women (68.4%) had undergone MRM surgery, and 37 (31.6%) had undergone BCT” in the "Results" section and present them in Table 1 in the manuscript. In addition, as mentioned in the "Results" section, the type of surgery did not have an effect on the QoL in this study (t=-0.288, p=0.774). To make this clearer and combine it with another reviewer’s suggestion, we changed the sentence in the revised manuscript as follows: “Other
characteristics and medical status factors were not predictors of the QoL, including age, educational level, tumor size, lymph node involvement, type of surgery, or time after surgery.” Please refer to the file.

Reviewer comments:
More importantly, it does not state whether the women has sentinel node biopsies vs axillary node dissections. The literature has shown that women with Axillary Node dissections had a lymphedema rate that ranged from 10-25%. This lymphedema has been markedly reduced in women with sentinel Node biopsies. The study should look at these factors and re-look at their stats and conclusions using the above distinctions

Authors response and revisions:
Thank you for the thoughtful comment. All recruited participants had received sentinel node biopsies and axillary node dissection. Sentinel node biopsy is a standard diagnostic procedure in Taiwan. To make this clearer and combine it with another reviewer’s suggestion, we changed the sentence in the "Methods" section in the revised manuscript as follows: “Inclusion criteria for the study were women: (1) with breast cancer who had received sentinel node biopsies and a pathological report indicating no distant metastasis and who had received axillary node dissection;...”

Reviewer comments:
Also, what are the symptoms that are being controlled? Pain? lymphedema? range of motion. The lymphedema will need to be evaluated in the context of the type of axillary surgery. There also is a longer period of time needed to evaluate the effects of lymphedema. The concept of earlier ROM exercises is impt but this study makes it difficult to assess the exact benefit

Authors response and revisions:
Thank you for the comments. The goal of this study was to investigate the mediating effect of performing shoulder-arm exercise 30 min/day on the postoperative severity of symptoms and QoL among patients with breast cancer who received axillary node dissection. We used the Symptom Distress Scale-Chinese Modified Form (SDS-CMF) to assess the severity of various symptoms, including numbness, lymphedema, restricted arm movement, etc. Also, because of the limitations of the study design and difficulties of recruiting participants, it is currently impossible for us to evaluate the effects of lymphedema over a longer period of time (more than 2 years). However, the literature states that lymphedema can occur a few days after surgery; therefore, it is important to begin ROM exercises early on. We included participants in the postoperative 2~4-month period and tried to evaluate the effects of the postoperative severity of various symptoms over a longer period of time. Further, based on another reviewer’s comment, we also stated this limitation in the revised manuscript in the "Limitations" section as follows: “the study's cross-sectional design prevented us from observing cause-effect relationships among symptom severity, regular shoulder-arm exercises, and QoL. Prospective studies are needed to confirm links of symptom severity (especially lymphedema) with regular shoulder-arm exercises and the QoL (as a primary endpoint) among women after breast cancer surgery.”
Reviewer 2

Reviewer comments :
The authors present a cross-sectional study analyzing the QOL of patients with breast cancer after surgery. The study compares the QOL of patients that followed shoulder exercises, and those that did not. The authors present an interesting article for many reasons. First of all, the authors tackle the subject of physical exercise, which the general public (including physicians) tend to consider useful and beneficial, while limited data on the topic exist in great cancer. Second, and most importantly, the authors present a study on QOL, which should be constantly encouraged nowadays, as QOL is one of the only 2 (along with OS) clinically relevant endpoints to the patients. As such, this paper, despite its many flaws, would be very interesting to the readers of BMC Women's Health.

Authors response and revisions :
Thank you for your comments.

Reviewer comments :
Introduction: plz shorten the intro as it is too lengthy, and the general idea of adverse events is redundant, a few sentences on common adverse events and decreased QOL would suffice.

Authors response and revisions :
According to the reviewer’s suggestions, we revised these sentences as follows: “The ability to perform activities of daily life (ADLs) and levels of functionality are essential to determining the QoL of breast cancer survivors. In particular, adverse effects of treatment (e.g., pain and fatigue) can interfere with one’s functional capacity (FC) and directly affect one’s QoL [5]. So, persistent FC and QoL should be discussed longitudinally among breast cancer patients after surgery, especially including all activities and exercises [6].”

Reviewer comments :
Methods: This is a cross-sectional study, so it would obviously carry a lot of limitations and bias, hopefully in the future prospective studies would be implemented. This is something that the authors should mention more clearly in their limitations, instead of only calling for new prospective study. It should be made clear that the study design is a limitation to the study. Also the conclusion should call for prospective QOL studies, as a primary endpoint.

Authors response and revisions :
Based on your comments and another reviewer’s comments, we revised and clarified this point in the "Limitations" section as follows: “the study's cross-sectional design prevented us from observing cause-effect relationships among symptom severity, regular shoulder-arm exercises, and QoL. Prospective studies are needed to confirm links of symptom severity (especially lymphedema) with regular shoulder-arm exercises and the QoL (as a primary endpoint) among women after breast cancer surgery.”

Reviewer comments :
Methods: any reason why the authors picked a 90% power? This is weird as the typical number used is 80%, maybe add a sentence on the reason for the 90% if anything relevant.
Thank you for this comment. We revised this part in methods section as follows: “To obtain a power of 0.80, with an effect size, \( F_2 \), of 0.15, alpha of 0.05, and number of predictors of 9, the sample size calculation for statistical significance with a linear multiple regression was performed. The total sample size needed was determined to be 114.”

Reviewer comments:
Methods: What are the 10 predictors that you assumed initially in your design?

Authors response and revisions:
Thank you for pointing out this omission. Nine predictors were assumed in this study, including severity of symptoms, performing the shoulder-arm exercise for 30 min/day, age, educational level, tumor size, lymph node involvement, type of surgery, time after surgery, and treatment received after surgery.

Reviewer comments:
Methods: FLIC, please change "person's" to "patient's QOL"

Authors response and revisions:
We changed this term in the revised manuscript

Reviewer comments:
Methods: is the FLIC validated in Breast cancer? Whether yes or no, it should be mentioned in text. And if not, should be added to the limitations too. It is okay to use non-validated tools since HRQOL are still relatively new, and thus any research on that filed should be encouraged. But if the tool is not validated it should be made clear.

Authors response and revisions:
The Chinese version of the FLIC had good validity and reliability for various cancer patients, including breast cancer patients (Fong, Lee, Tung, Wong, Chan, Goh, & Cheung, 2014). To make this clearer, we revised this point in the"Methods"section as follows: “The Chinese version of the FLIC had strong psychometrics for various cancer patients, including breast cancer patients [14,16].”

We also added this reference to the revised manuscript.

Reviewer comments:
Methods: same question for SDS-CMF.

Authors response and revisions:
Thank you for the comment. To make this clearer, we revised this point in the"Methods"section as follows: “The SDS-CMF had strong psychometrics for breast cancer patients [14,17].”
Reviewer comments:
Discussion: It would be interesting if the authors could add few points on how QOL are being implemented. QOL are - in the majority of trials - included as secondary endpoints only. While in reality, OS and QOL are the only 2 clinically relevant patients endpoints. As such, one or those 2 endpoints should always be a primary endpoint in any clinical trial. More importantly, any trial that is practice changing should be based on one of those 2 endpoints, and not surrogate endpoints, like the most commonly used PFS. The authors could add those points mainly focusing on QOL, and add some citations.

Authors response and revisions:
We appreciate the reviewer’s thoughtful comments. Accordingly, we added the following points to the revised manuscript: “In a majority of trials, QoL is only included as a secondary endpoint [23]. In reality, QoL is one of only two clinically relevant patient endpoints [24]. As such, the QoL endpoint should always be a primary endpoint in any clinical trial. More importantly, any trial that evaluates changes in practices should be based on QoL endpoints, and not surrogate endpoints, like the most commonly used progression-free survival (PFS).”
We also added the following references to the revised manuscript.

Reviewer comments:
Limitation: a major limitation to be added is the lack of comparator and baseline in the study, which severely limits the interpretation of QOLs. Simply comparing QOL numbers at one time point between two groups (shoulder exercise vs No exercise) is definitely not enough to draw conclusions. The validity of QOL measurement tools is quite complex, and depends on many factors, including multiple time points, and MID, issues that are not tackled at all bu the authors.

Authors response and revisions:
Thank you for these thoughtful comments. We added this limitation to the revised manuscript as follows: “this study lacked baseline data and a comparator, which severely limit interpretation of the QoL. Well-designed and well-executed clinical trials are needed to draw convincing conclusions.”

Reviewer comments:
Conclusion: the conclusion and take-home message should be toned down. This study is nice, however, the study suffers from extensive limitations, and thus any conclusion is questionable. Using "could" and "may"... would be better in the conclusion, as a clear indication cannot be induced from this study. It is fine to have questionable outcomes, however this should be made clear, rather than stating strong conclusions, that readers might simply take for granted. This comment also applies to the conclusion in the abstract.

Authors response and revisions:
Thank you for these comments. We used “could” and “may” in the revised manuscript in both the "Conclusions" and "Abstract". Please refer to the file.
Reviewer comments:
Conclusion: The call for future research should focus mainly on prospective, multiple-time points and follow-ups QOL studies, mediators like KPS would be less interesting, as the complete purpose of QOL, is to be a stand alone endpoint. Another really interesting call, would be to include more studies (mainly clinical trials) where QOL is a PRIMARY endpoint, and not just a secondary endpoint.

Authors response and revisions:
According to the reviewer’s comments, we revised and added the following sentences: “Future studies can focus on prospective follow-up QoL studies, with larger sample sizes and multiple-time points. In addition, more studies (mainly clinical trials) need to include QoL as a primary endpoint, and not just as a secondary endpoint.”

Reviewer comments:
Tables: Could the authors specify individual T, and N stages (no need for M, as no metastatic patients were recruited) instead of clumping them together into the composite stage? Adding tumor size (T), lymph node involvement (N) alone would be a better way to understand the population. Especially N stage, as N stage play a big role on management, and subsequent adverse events.

Authors response and revisions:
We revised tumor size (T) and lymph node involvement (N) separately in Table 1 as well as in the content of the revised manuscript. Also, the T (F=0.668, p=0.515) and N (t=0.304, p=0.761) variables were not predictors of the QoL. Please refer to the file.

We hope these revisions will meet all the guidelines of BMC Women’s Health and those of the reviewers. We did our best to modify our paper and exhibit its uniqueness. Thank you again for your kind efforts on our behalf.

Sincerely,

Shu-Fen Kuo