

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Association between hand grip strength and impaired health-related quality of life in Korean cancer survivors: a cross-sectional study
<b>AUTHORS</b>	Paek, Jeongki; Choi, Yoon Ji

## VERSION 1 - REVIEW

<b>REVIEWER</b>	Young Sik Park Seoul National University Hospital, Korea
<b>REVIEW RETURNED</b>	25-Apr-2019

<b>GENERAL COMMENTS</b>	<p>The authors present the positive association between HGS and HRQoL using KNHANES VI-VII data. I think there are some limitations about this manuscript.</p> <p>Major points</p> <p>1. About study population The authors focused on 'cancer survivor'. I think the background hypothesis of the authors is the mean HGS of cancer survivors would be lower than general population (2nd paragraph of discussion section, p15). But the mean HGS is not different between cancer survivor and general population. According to these results (this manuscript, ref 18 and ref 19), I wonder the association between HGS and HRQoL in the entire population (KNHANES VI-VII). If the results are same, I think it can be a general phenomenon, not specifically to the cancer survivors.</p> <p>2. What is the definition of 'cancer survivor'? There is no definition of cancer survivor. Only Fig 1 shows the definition. The study population of this study is 'cancer survivor', so detailed information should be needed in the method section. Roughly, I think there are two groups in the cancer survivors, such as with cancer vs. without cancer or under active treatment vs. under surveillance. And as I know, this information can be obtained from the KNHANES data. Detailed information and further analysis are needed.</p> <p>3. HGS is associated with muscle power. Generally, tall or heavy weighted people are stronger than short or light weighted people. According to table 1, Height and Weight are significantly different between normal and weak HGS, but BMI is not. It is because BMI means fatness, not muscle strength.</p>
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	<p>In multivariable analysis, there is no factor which might be associated with muscle power. But BMI is included. I cannot understand.</p> <p>Minor points</p> <ol style="list-style-type: none"> <li>1. In table 1, please put the unit in the appropriate line, such as “(%)” after Residence, Marital status etc.</li> <li>2. In figure 1, “study population” are used in the 2nd and 3rd boxes. I would recommend to use different term, such as eligible population in the 2nd and study population in the 3rd.</li> </ol>
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<b>REVIEWER</b>	Shinichiro Morishita Institute for Human Movement and Medical Science, Niigata University of Health and Welfare. Japan.
<b>REVIEW RETURNED</b>	11-May-2019

<b>GENERAL COMMENTS</b>	<p>Author assessed the association between hand grip strength (HGS) and health-related quality of life among Korean cancer survivors. The topic addressed is interesting and deserves a constructive discussion for cancer survivors. The statistics used are appropriate and the conclusions derived from these and the interpretations of the spatial images are consistent and sound.</p>
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<b>REVIEWER</b>	Kyuwan Lee University of Southern California
<b>REVIEW RETURNED</b>	23-Jun-2019

<b>GENERAL COMMENTS</b>	<p>While this manuscript includes an important topic, it was not scientifically reported and multiple flaws and uncertainty were of major concerns as reviewed. Even abstract and strength were not sufficiently clear and hard to understand what the authors attempt to state. Here are the comments from reviewing this manuscript.</p> <p><b>Abstract</b></p> <p>Setting needs to be more specific, particularly where the outcome variables were measured</p> <p>Participants: Cancer survivors needs more information, i.e. stage, cancer type and etc.</p> <p>Primary outcome measures: ‘normal and weak’ is not needed here since it causes confusion. Or needs explanation how normal and weak were defined. Further if the prevalence of impaired HRQOL by HGS is the primary outcome, the title needs to be changed to represent this.</p> <p>Secondary outcome measures: estimated risk of impaired quality of life by HGS is not clear. May need rewording to clarify.</p> <p>Results: It is unclear what ‘the prevalent cancer site was the stomach’ mean. Does this mean the percentage out of 1,037 cancer survivors?</p> <p>Since weak and normal HGS are mainly explained in the results of abstract, it is recommended that the authors state how the normal and weak HGS were defined.</p> <p>It is unclear what the risk of impaired HRQoL means; What the risk of impaired HRQoL.</p> <p><b>Strength and Limitations of this study</b></p> <p>Firstly, this may not be true since there are many studies showing the association between HGS and HRQoL in cancer survivors.</p>
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	<p>Here is one example published in 2013 Support Care Cancer. 2013 Dec;21(12):3261-70. doi: 10.1007/s00520-013-1894-4. Epub 2013 Jul 20.</p> <p>Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. Second, this is not really a large population based study since it includes only the sample size of 1,037 survivors. Third the use of multiple logistic regression cannot be strength or limitation since it is how the analysis was performed. There is no novelty or innovative features.</p>
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<b>REVIEWER</b>	Jennifer Bail University of Alabama at Birmingham USA
<b>REVIEW RETURNED</b>	09-Jul-2019

<b>GENERAL COMMENTS</b>	Very well written article on an important subject.
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### VERSION 1 – AUTHOR RESPONSE

Responses to the comments of Reviewer: 1

We appreciate that the reviewer's comments. The followings are point-by-point responses:

Major points

#### 1. About study population

The authors focused on 'cancer survivor'. I think the background hypothesis of the authors is the mean HGS of cancer survivors would be lower than general population (2nd paragraph of discussion section, p15). But the mean HGS is not different between cancer survivor and general population. According to these results (this manuscript, ref 18 and ref 19), I wonder the association between HGS and HRQoL in the entire population (KNHANES VI-VII). If the results are same, I think it can be a general phenomenon, not specifically to the cancer survivors.

Response: Thank you for providing these insights. We fully agree with the opinion that an analysis of the general population should be included. We have analyzed the general population in KNHANES VI-VII and added the figures to Figure 2. This point added to discussion section. Flow diagram of participant selection (Figure 1) were also revised.

#### 2. What is the definition of 'cancer survivor'?

There is no definition of cancer survivor. Only Fig 1 shows the definition. The study population of this study is 'cancer survivor', so detailed information should be needed in the method section.

Roughly, I think there are two groups in the cancer survivors, such as with cancer vs. without cancer or under active treatment vs. under surveillance. And as I know, this information can be obtained from the KNHANES data.

Detailed information and further analysis are needed.

Response: We agree that there was not enough description for 'cancer survivor'. We have added the sentence for definition of cancer survivor in introduction and method as follows: "Cancer survivor is defined as person who have been diagnosed with cancer of any type, including before, during and after treatment." in page 6. "Adults who have been diagnosed with any type of cancer by a physician were included in this study as cancer survivor." in page 7.

3. HGS is associated with muscle power. Generally, tall or heavy weighted people are stronger than short or light weighted people. According to table 1, Height and Weight are significantly different between normal and weak HGS, but BMI is not. It is because BMI means fatness, not muscle strength.

In multivariable analysis, there is no factor which might be associated with muscle power. But BMI is included. I cannot understand.

Response: We agree with the opinion that it is reasonable that height and weight are included in the multivariable analysis rather than BMI. The multivariable analysis was conducted again according to the reviewer 1's opinion, and the Table 2. was revised.

#### Minor points

1. In table 1, please put the unit in the appropriate line, such as "(%)" after Residence, Marital status etc.

Response: We have added the unit in the table 1 as the reviewer suggested.

2. In figure 1, “study population” are used in the 2nd and 3rd boxes. I would recommend to use different term, such as eligible population in the 2nd and study population in the 3rd.

Response: We follow the reviewer’s suggestion.

Responses to the comments of Reviewer: 2

We appreciate that the reviewer’s comments.

Responses to the comments of Reviewer: 3

We appreciate that the reviewer’s comments. The followings are point-by-point responses:

Abstract

Setting needs to be more specific, particularly where the outcome variables were measured

Response: We have described in more specifically the information about setting according to Review 3’s opinion.

Participants: Cancer survivors needs more information, i.e. stage, cancer type and etc.

Response: We have added more detailed descriptions for the definition of cancer survivor as follows: “(person with cancer of any type who is still living)” in participants part of the abstract.

Primary outcome measures: ‘normal and weak’ is not needed here since it causes confusion. Or needs explanation how normal and weak were defined.

Response: As reviewer 3 pointed out, we have deleted “(normal and weak)”.

Further if the prevalence of impaired HRQOL by HGS is the primary outcome, the title needs to be changed to represent this.

Response: We agree with reviewer 3’s opinion. We added “impaired” to the title to more clearly indicate the direction of this paper as follows: “Association between hand grip strength and impaired health-related quality of life in Korean cancer survivors: a cross-sectional study”

Secondary outcome measures: estimated risk of impaired quality of life by HGS is not clear. May need rewording to clarify.

Response: We have deleted “secondary outcome measures” because it was not clear as the Reviewer 3 has pointed out.

## Results

It is unclear what ‘the prevalent cancer site was the stomach’ mean. Does this mean the percentage out of 1,037 cancer survivors?

Response: We intended to explain “which cancer sites more appeared in study population”, but it was not clear. We have revised the sentence to make it clearer as follows: ‘In study population, the most common cancer site was the stomach, followed by the thyroid, breast, colorectal, and cervix.’

Since weak and normal HGS are mainly explained in the results of abstract, it is recommended that the authors state how the normal and weak HGS were defined.

Response: There are some studies reporting HGS reference values, but it is not established yet. According to European working group on sarcopenia (EWGSOP2), low muscle strength using cut-off point for HGS is defined as <27 kg in men and < 16kg in women. Low muscle strength of HGS in the Asian Working Group for Sarcopenia (AWGS) is defined as < 26 kg in men and < 18kg in women. We used the manner of previous study (reference 20) to classify the normal and weak HGS group as the lowest quintiles (<29.7 kg in men and <19.7 kg in women). This is described in the results part of abstract as follows: “weak HGS according to gender-specific cut-off values (lowest quintile; <29.7 kg in men and <19.7 kg in women).”

It is unclear what the risk of impaired HRQoL means; What the risk of impaired HRQoL.

Response: We agree with reviewer 3's opinion. We have removed it because the word “risk of” makes the meaning obscure. Also, we have added descriptions for the definition of impaired HRQoL in results part of abstract as follows: “(some or extreme problem in EuroQol-5 dimension)”

#### Strength and Limitations of this study

Firstly, this may not be true since there are many studies showing the association between HGS and HRQoL in cancer survivors. Here is one example published in 2013 Support Care Cancer. 2013 Dec;21(12):3261-70. doi: 10.1007/s00520-013-1894-4. Epub 2013 Jul 20.

Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients.

Response: As the reviewer 3 pointed out, 1st sentence of the strengths and limitations was likely to inappropriate. In a broad sense, advanced cancer patients who have recently received inpatient treatment also belong to cancer survivors. However, the study is not in line with our research direction. We are assumed that most cancer survivors who participated in KNHANES are no differences with the outwardly healthy population. Our hypothesis is that weak HGS is associated with impaired HRQoL even in “near healthy” cancer survivors who no longer receive active cancer treatment and are no longer followed up. Nevertheless, the sentence was inappropriate and was

therefore amended as follows: This study identified that weak hand grip strength (HGS) is associated with impaired HRQoL in cancer survivors.

Second, this is not really a large population based study since it includes only the sample size of 1,037 survivors.

Response: We generally agree with reviewer 3's opinion. However, KNHANES is one of the most nationally representative and structured data in Korea, and we analyzed all data including HGS. Because HGS measurement is not routine practice, it is difficult to generate large amounts of data. However, it could be subjective, we address only the quality of data rather than size. 2nd sentence of the strengths and limitations was revised as followed: The data used in this study were derived from nationally representative and well-designed systematic surveys.

Third the use of multiple logistic regression cannot be strength or limitation since it is how the analysis was performed. There is no novelty or innovative features.

Response: As reviewer 3 pointed out, we have deleted 3rd sentence of the strengths and limitations.

Responses to the comments of Reviewer: 4

We appreciate that the reviewer's comments.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Kyuwan Lee University of Southern California, United States
<b>REVIEW RETURNED</b>	29-Jul-2019
<b>GENERAL COMMENTS</b>	Improved and addressed concerns after revision.