Author's response to reviews

Title: Oxidative stress level is not associated with survival in terminally ill cancer patients: a preliminary study

Authors:

Chang Hwan Yeom (lymphych@hanmail.net)
Youn Seon Choi (younseon@korea.ac.kr)
Hong Yup Ahn (ahn@dongquk.edu)
Su Hey Lee (ilohyang@hanmail.net)
In Cheol Hwang (spfe0211@gmail.com)

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Author's response to reviews: see over
Response to Reviewer #1

Comment #1: Elucidate for excluding delirious patient and symptom/performance assessments

Thank you for bringing this to our attention. We described more detail what you indicated, as follows:

Method section (page 3-4)

Design and Subjects

No subject included in the study had taken a vitamin supplement during the two days before enrollment, had received a blood transfusion or albumin during the one week before enrollment, had a chronic kidney disease, or had a hematologic malignancy. In addition, subjects were not eligible to participate if they were not capable of communicating with a physician or were not competent enough to understand the aim of the study.

Clinical examination

Data on demographics and clinical information were collected by an experienced palliative care team of physicians and registered nurses: included information were age, sex, cancer site, Eastern Cooperative Oncology Group (ECOG) performance status, palliative prognostic score [6], presence of fever and anorexia, and evidence of infection. The ECOG performance status is an observer-rated scale of patient physical ability using numbers ranging from 0 (able to carry out all normal activities) to 4 (completely disabled) [7]. Anorexia was defined as less than five spoons per meal (about one-third amount of routine meal). Patients also provided clinical information on average pain score by numerical rating scale and presence of some symptoms (dysphagia and dyspnea on exertion). Dysphagia and dyspnea were determined by the following yes-no question: “In the past 24h, have you been difficult to swallow/short of breath on exertion?” Survival times were measured from the date of enrollment in the study.

Comment #2: Possible pre-estimation of sample size

We thank the reviewer for this comment which we never noticed. We deleted the following statement in limitation; ‘Because there were no other reported studies investigating prognostic values of serum vitamin C or OS within this population [5, 21], we could not estimate the appropriate sample size.’

Comment #3: Report the 95% CI for survival time and number of patients being alive/dead

We agree with this recommendation. We presented the number of patients in a new figure (study flowchart), and added the 95% CI in Table 1 (page 12) and Results section (page 5).

Comment #4: Provide a breakdown of palliative prognostic score in Table 1

Thanks for this comment. According to the manual of palliative prognostic score, we classified into 3 groups based on the 30-day survival probability, as follows:

<table>
<thead>
<tr>
<th>Palliative prognostic score</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5.5</td>
<td>25 (38.5)</td>
</tr>
</tbody>
</table>
**Comment #5:** Clarify the descriptive statistics of laboratory findings in Table 1

We are really sorry for this missing point. We marked the superscript “a” (expressed as median and IQR) in Table 1 (page 12-13).

**Comment #6:** Report the median survival in Table 2

We absolutely subscribe this opinion. According to the reviewer’s comment, we reconstructed Table 2 (page 14-16).

**Comment #7:** Provide an associations of oxidative stress status with vitamin C level, CRP level, and palliative prognostic score

We agree with this suggestion. We have already described indirectly the relations of oxidative stress to vitamin C and CRP level in Table 3. We added the palliative prognostic score, as follows; Table 3 (page 17)

<table>
<thead>
<tr>
<th>Higher oxidative stress (≥ median, 412.9 U.F.)</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palliative prognostic score (≥ 7.5&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>1.20</td>
<td>0.45-3.18</td>
<td>0.714</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High&lt;sup&gt;a&lt;/sup&gt; C-reactive protein</td>
<td>1.54</td>
<td>0.58-4.10</td>
<td>0.385</td>
</tr>
<tr>
<td>Low&lt;sup&gt;a&lt;/sup&gt; vitamin C</td>
<td>0.74</td>
<td>0.28-1.95</td>
<td>0.537</td>
</tr>
</tbody>
</table>

*Based on the median value.

**Comment #8:** Revise the abstract: (i) revise the term “performance”, (ii) more in depth reporting of key findings, (iii) adding statistic methods

Thanks for these comments. With comments of you and another reviewer, we revised the abstract, as follows;

Abstract section (page 2)

**Background**

While cancer patients have higher oxidative stress (OS) and lower antioxidant activity, evidence for the association of these parameters with survival in patients with terminally ill cancer is lacking.

**Methods**

We followed 65 terminal cancer patients prospectively. We assessed their performance status, some symptoms, and serum levels of vitamin C and OS level. The Gehan’s generalized Wilcoxon test was used to examine the association between survival times and variables.
Results
Subjects’ performance was very poor and they had a high level of OS and a low level of vitamin C. No significant association of these two parameters with survival time was noted (p-value, 0.637 for high OS and 0.240 for low vitamin C). Poor performance status was independently related to high OS status after adjusting for potential confounders (adjusted OR, 4.45; p-value, 0.031).

Conclusions
In terminally ill cancer patients at the very end of life, the prognostic role of OS for survival requires further study.

Comment #9: Study flow chart
Thanks for this recommendation. We constructed a new figure (Figure 1 - Flowchart of patient recruitment), and describe it as follows;

Method section (page 3)

Design and Subjects
This prospective observational study was carried out at two hospice-palliative care units. From January 2012 to June 2012, we identified 296 consecutive terminal cancer patients who were admitted to facilities. A terminal cancer patient was defined as someone with progressive advanced cancer for whom conventional anticancer therapy was no longer indicated [1]. No subject included in the study had taken a vitamin supplement during the two days before enrollment, had received a blood transfusion or albumin during the one week before enrollment, had a chronic kidney disease, or had a hematologic malignancy. In addition, subjects were not eligible to participate if they were not capable of communicating with a physician or were not competent enough to understand the aim of the study. Data of 65 patients were analyzed finally and a flowchart of patient recruitment depicted in Figure 1.

Comment #10: More in depth discussion of the major findings
Thanks for this great comment. According to the reviewer’s comment, we added the following statement;

Discussion section (page 6)

It is well known that cancer patients are characterized by higher levels of OS markers and lower levels of serum vitamin C than healthy controls; there is a scarcity of literature addressing the association with survival of advanced cancer patients at the end of life [11]. Mayland et al [5] reported that low plasma vitamin C concentrations were associated with shorter survival in terminally ill cancer patients. But those findings were not confirmed by multivariate analysis and they did not address the level of OS, which could be a predictor of cancer-specific survival [12]. In the current study, we failed to examine the prognostic significance of serum vitamin C or OS on survival. The lack of significance could be due to (i) true negative finding: these parameters are not helpful to discriminate the patients with a short survival, or (ii) false negative findings: small sample size or artificial cutoff value.
Response to Reviewer #2

Comment #1: Note a limitation for not using a validated symptom assessment tool
Thank you for bringing this to our attention. We acknowledged this limitation additionally, as follows;
Discussion section (page 7)

Finally, some symptoms such as anorexia, dysphagia and dyspea on exertion were not evaluated by a validated symptom assessment tool.

Response to Reviewer #3

Comment #1: Revise title
We subscribe to this opinion. We revised title, as follows;
Title Page (page 1)

Oxidative stress is not associated with survival in terminally ill cancer patients: a preliminary study

Comment #2: Delete “performance” in background and conclusions of abstract
We agree with this opinion. We deleted “performance” in background and revise conclusions, as follows;
Abstract section (page 2)

Conclusions
In terminally ill cancer patients at the very end of life, the prognostic role of OS for survival requires further study.

Comment #3: Include OR and p-values in results of abstract
Thanks for this comment. We included OR and p-values in results of abstract, as follows;
Abstract section (page 2)

Results
No significant association of these two parameters with survival time was noted (p-value, 0.637 for high OS and 0.240 for low vitamin C). Poor performance status was independently related to high OS status after adjusting for potential confounders (adjusted OR, 4.45; p-value, 0.031).

Comment #4: Clarify 1st sentence of background paragraph 2
Thanks for this comment. We revised this sentence, as follows;
Background section (page 2)

Patients with malignant tumors have higher oxidative stress (OS) by tumor growth itself and/or increased systemic inflammatory response.