Author's response to reviews

Title: A proposed prognostic 7-day survival formula for patients with terminal cancer

Authors:

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Author's response to reviews: see over
August 24, 2009

Andrea Bucceri Ph.D.
Scientific Editor, BMC

Dear Dr. Bucceri:

Thank you for your kind announcement of review of our manuscript, “A proposed prognostic 7-day survival formula for patients with terminal cancer,” which my colleagues and I here submit for your further consideration for inclusion in your journal. We are grateful for the input of your two reviewers, whose insights, we think, have added immensely to the effort. We sincerely thank the reviewers for their comments and below enclose our point by point response to their concerns.

We hope you find our revised manuscript acceptable for publication in your journal. Should you have any questions, please do not hesitate to contact me.

Yours sincerely,

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Comments from Editor:

1. The following formatting changes should also be made:

1) **Informed consent must be documented** in the Methods section. Manuscripts may be rejected if the editorial office considers that the research has not been carried out within an ethical framework, e.g. if the severity of the experimental procedure is not justified by the value of the knowledge gained.

   **Author:** YES, Informed consent was obtained. Thank you for pointing this out. We have added a statement to this effect so as to clear up any misunderstanding.

2) Please rename the "CONTRIBUTION STATEMENT" as "Authors' Contributions"

   **Author:** The section has been renamed.

3) Please rename the "Conflict of Interest" section as "Competing Interests" and move it down before the Authors' Contributions section.

   **Author:** The name of the section has been changed and moved. Thank you for pointing this out.

4) Please move the Acknowledgements section before the reference list and after the "Authors' Contributions"

   **Author:** The section has been moved. Thank you!

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**No.1 Reviewer's report:**

Major compulsory revisions

1. I appreciate that this study was approved by the Institutional Review Board of Buddhist Dalin Tzu Chi General Hospital. Nonetheless this study does raise some ethical challenges which I think the authors should discuss. **Was informed consent obtained from patients?** and if not why not? Although this is an observational study the authors have collected data (from both competent and incompetent patients) that would not routinely be recorded from such patients (at least not in UK practice). Would the authors have obtained blood specimens (and undertaken other study procedures) from all patients if they had not been involved in the study? And, if not, then they need to justify why consent was not obtained.

   **Author:** Yes, we had informed consent given by each participant. Then we performed our observational study. Because hospice care in Taiwan is hospital-based, the laboratory variable (blood specimens) and clinical variables were routinely checked in our routine practice. In other words, we did obtain blood specimens and undertaken
other study procedures from all patients in the regular course of their hospital stay, and would have done so, even if they had not been involved in the study.

2. In Table 4 it is indicated that some data is missing from the validation set - but it is not specified which data is missing. Moreover there is no data obviously missing from Table 1 (which also refers to the validation set)

**Author:** There was no missing data for Training group in Table 1 and Table 4. However, for the Validation group, there were missing data in several variables of Table 1 as follows:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Actual number of data</th>
<th>Number of missing data</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>352</td>
<td>1</td>
</tr>
<tr>
<td>Hb</td>
<td>352</td>
<td>1</td>
</tr>
<tr>
<td>Platelet</td>
<td>352</td>
<td>1</td>
</tr>
<tr>
<td>Glucose</td>
<td>352</td>
<td>1</td>
</tr>
<tr>
<td>BUN</td>
<td>352</td>
<td>1</td>
</tr>
<tr>
<td>Creatinine</td>
<td>350</td>
<td>3</td>
</tr>
<tr>
<td>SGOT</td>
<td>349</td>
<td>4</td>
</tr>
<tr>
<td>SGPT</td>
<td>346</td>
<td>7</td>
</tr>
<tr>
<td>Albumin</td>
<td>346</td>
<td>7</td>
</tr>
</tbody>
</table>

Some data were missing from the validation set in Table 4 as well. The total number of patients in the Validation set was 349 instead of 346. The missing data included one for BUN and three for Respiration rate.

We have indicated where variables have missing data in the footnotes to Table 1 and Table 4, and revised the sample size of the validation set in Table 4.

3. No data is provided on the number of eligible patients admitted to the unit who were not included in the study...it may be that all eligible patients were included in the study (which raises again the issue of consent).

**Author:** For the training group, number of admission during the study period was 415 cases, of which 374 cases were enrolled (91%). For the Validation group, the number of admissions during the study period was 430 cases, of which 353 cases were enrolled (82%). Overall percentage of enrollment was 86%. Most cases not enrolled were due to admission during a holiday or weekend.
This statement has been included in the Materials and Methods section to clarify.

5. No data is provided on how frequently symptoms were assessed by carers rather than by patients and no discussion is had about this may have affected results or usefulness of the scale in clinical practice.

**Author:** A limited number of patients were assessed by family caregivers rather than by patients due to the cognitive impairment. The proportion of unconscious patient in Training group is 4.8%. (Cognitive impairment=3, 18/374=4.8%)

<table>
<thead>
<tr>
<th>Cognitive</th>
<th>Number of case</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>273</td>
</tr>
<tr>
<td>1</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>374</td>
</tr>
</tbody>
</table>

The proportion of unconscious patient in Validation group is 8.2%. (Cognitive impairment=3, 29/353=8.2%)

<table>
<thead>
<tr>
<th>Cognitive</th>
<th>Number of case</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>228</td>
</tr>
<tr>
<td>1</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>353</td>
</tr>
</tbody>
</table>

We have included this information in the “Data collection” section and included it as a limitation at the end of Discussion section.

6. Why is there no missing data from the training set? Surely some patients must have died before study assessments were undertaken?

**Author:** We collected these data within 24 hours of admission. Therefore, there is no missing data because the patients died in the training group. We did have missing data in the validation group, as previously discussed.

Minor essential revisions
1. In results section... “The survival rates were significant difference between the training and validation groups.” should read "SIGNIFICANTLY DIFFERENT"
Author: The error has been corrected. Thank you.

2. In results section..."The training and validation groups differed significantly in cognitive status, ECOG score, and ascites (P<0.05).” DELETE COMMA
Author: The error has been corrected. Thank you.

Discretionary revisions
1. The authors refer to Chuang’s prognostic score and Bozcuk’s intrahospital cancer mortality risk model as being the most recent additions to prognostic literature (both published in 2004). Have the authors undertaken a more recent literature search? I am personally aware of at least three other studies/papers that have been published in the last couple of years and suspect there may be some more...

Author: Most recently, Chow’s predictive model [Chow et al., 2008], Stone’s prognostic scale [Stone et al., 2008], Chuang’s prognostic score [20] and Bozcuk’s intrahospital cancer mortality risk model [21] were developed to predict survival, and the latest three are for short-term survival. Of these, Chow’s predictive model of the three-variable number of risk factors (NRF) — nonbreast cancer, metastases other than bone and Karnofsky performance score <60 — is clinically simple and user-friendly. For 3-month survival, this model estimates probability of patients with NFR<1, NFR=2, NFR=3 were 83%, 76%, and 44% respectively, in external validation set. In this model, all subjects were attending a palliative radiotherapy clinic. Stone’s prognostic scale uses four variables: primary lung cancer, secondary liver cancer, C-reactive protein, and poor performance status (ECOG=4) to predict 14-day survival. Stone’s prognostic scale would have more value for identifying those patients not suitable for hospice admission, due to high predictive value (85%), and low positive predictive value (39%). By contrast, Kelly’s model suggested C-reactive protein as the simple prognostic indicator in patients with advanced cancer [Kelly et al., 2007]

We have rewritten the paragraph that began on page12 based on the new information and additional references.

2. There is really quite a marked difference in the ECOG performance status scores in the development and the validation sets? It seems too large a difference to be chance alone (although, of course, this could explain it). Was there any change in admission procedures to the unit between the two data collection periods? The authors should discuss how this difference in ECOG profiles may have affected their results.
Author: There was no bias either in admission procedures or data collection. We did find a significant difference in ECOG between the training group and validation group over 7 days (p<0.001). In contrast, there was only marginal difference in ECOG between two groups within 7 days. Despite the difference in ECOG between the two groups, we still found good sensitivity and specificity for the validation group using our predictor model.

<table>
<thead>
<tr>
<th></th>
<th>&gt;7 day</th>
<th>Within 7 day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Training group</td>
<td>Validation group</td>
</tr>
<tr>
<td>ECOG (1, 2)</td>
<td>152</td>
<td>23</td>
</tr>
<tr>
<td>ECOG (3, 4)</td>
<td>131</td>
<td>263</td>
</tr>
</tbody>
</table>

No. 2 Reviewer's report

Major Compulsory Revisions
1. The rational for survival prediction in general is well known. Initiating palliative care "in time" is very important. It is for me not clear why palliative care should be starting up in the "last 7 days" of life. For most patients this is too late in the disease process. Probably the researchers mean "end-of-life" care, as is targeted by e.g. initiating the Liverpool Care Pathway for the dying in the last 48h of life. The rational why short-term/7 days survival prediction is important should be made more clearly.

Author: In Taiwan, between 2000 and 2004, the rates of late referrals for hospice care as a whole were 25.3%-28.9%, which were lower than the national statistics from the United State (35.1%), but higher than other published study reports (15.6%-20%) [Tang ST et al., 2007]. Furthermore, evidence suggests that late hospice referral increase the risk of a major depressive disorder in the first year of bereavement [Bradley et al., 2004]. When patients were enrolled in hospice with less than 7 days, hospice team often did not have adequate time to become familiar with patients and their home situation. The goal for comprehensive care (including the patients’ wish such as to die at home) might become impossible to fulfill [Miller SC et al., 2003]. Part of the explanation for late referral can be attributed to difficulties in establishing an accurate prognosis [Glare P et al., 2003].

References:

As per the note below to restrict the Discussion section to items pertaining to new findings, we have included this explanation in the Introduction section, and added the additional references to the References List.

2. The main literature review is being presented (and discussed) in the Discussion section, this should move to the Introduction; and only discussed in relation to findings in the Discussion section.
   **Author:** We have moved the details about other scales and measured into the Introduction, reserving the Discussion section based on reviewer’s comment. Thank you!

3. Abstract should be restructured: parts of methods are now presented in the background, and part of results are presented in Methods section. Real background, why the authors want to develop a 7day prognostic scale, is missing.
   **To Editor:** We have re-edited the Abstract based on the reviewer’s insights. Thank you!

4. In the discussion, the authors have to evaluate more clearly what the study results add to the existing knowledge of prediction models.
   **Author:**
   This scale is an important improvement over previous methods. First, every terminally ill cancer patient receives the probability of 7-day survival within 24 hours of admission by our prognostic scale. The reader can use the method indicated in the **supplementary information** to calculate the probability. Second, we have identified a laboratory factor (BUN) and patient vital sign (respiratory rate) as additional prognostic parameters. Thirdly, this prognostic scale shows relatively high sensitivity (80.9%) and negative predictive value (91.7%) for predicting 7-day survival among terminal cancer patients. This means that our prognostic scale has more value for identifying those patients not late referral for hospice care than for positively identifying those patients within 7 days of death.

   We now include this clarification in the Discussion section.
Supplementary Information

1. Excel file for calculating the probability.
2. Code for R to calculate the possibility

Based on the model listed in manuscript:

\[
\log \left[ \frac{\text{probability of dying within 7 days}}{1 - \text{probability of dying within 7 days}} \right] = \\
[-5.37 + 0.864*\text{cognitive status} (1 \text{ if cognitive=}0, \ 0 \text{ if otherwise}) + 0.782*\text{edema} (1 \text{ if edema=}0, \ 0 \text{ if otherwise}) + 1.208*\text{ECOG} (1 \text{ if ECOG=}1 \text{ and } 2, \ 0 \text{ if otherwise}) + 0.022*\text{BUN} + 0.104*\text{respiratory rate}].
\]

Please download the free statistical software: R, the latest edition is 2.9.1

Form http://www.r-project.org.

Fill out the data for each case you want to calculate the probability of within 7 days

\[
\text{yhat} \leftarrow (-5.37 \# \text{constant} \\
+ 0.864*1 \# \text{cognitive status} (1 \text{ if cognitive=}0, \ 0 \text{ if otherwise}), \text{here for example} =1 \\
+ 0.782*1 \# \text{edema} (1 \text{ if edema=}0, \ 0 \text{ if otherwise}), \text{here for example} =1 \\
+ 1.208*1 \# \text{ECOG} (1 \text{ if ECOG=}1 \text{ and } 2, \ 0 \text{ if otherwise}), \text{here for example} =1 \\
+ 0.022*20 \# \text{the value of BUN, here for example} =20 \\
+ 0.104*16) \# \text{respiratory rate per minute, here for example} =16
\]

\[
\text{phat} \leftarrow 1/(\exp(-\text{yhat})+1)
\]

\[
\text{phat} \# \text{then copy these syntax and paste on the R console}
\]
You can follow this easy method to estimate more accurately the probability of 7-day survival.

Minor Essential Revisions
1. Introduction. **Reference is missing** for the statement on "when patients' laboratory data and clinical symptoms and signs are added, an accurate prediction of survival in terminal cancer patients can be enhanced"
   **Author:** The paragraph has been rewritten as “In several major studies, some laboratory parameters have been shown to be capable of providing additional prognostic information (Maltoni et al., 2002)”

2. Introduction. What does an hospice in Taiwan means? is it an inpatient unit in a hospital or outside the hospital?
   **Author:** In Taiwan, hospice care includes inpatient hospice care and hospice home care. In Taiwan, in 2004, overall utilization of hospice care is 15.4%, and hospice home care only is 2.6%, inpatient hospice care only is 10.1%, and both home care and inpatient care is 2.8%. Our study was inpatient hospice care [Tang ST et al., 2007].
   We now include this clarification in the Introduction.
3. Introduction. Aim of study: what do you mean by "timely" referrals to palliative care?

“This study aimed to develop a validated model for 7-day survival prediction for terminal cancer patients to make more accurate prediction of short-term survival in order to facilitate timely referrals to palliative care as well as comprehensive care for terminally cancer patients.”

Author: Palliative care seeks to fulfill the needs of patients at the end of life. Ascertaining and carrying them out (e.g., the desire to die at home) requires the ability to predict short term survival.

We now include this explanatory note before our statement of the purpose of the study.

2. Methods. Ethical review of the study should be stated more clearly.

Author: We have re-edit the statement regarding Ethical review to clarify that all patients gave informed consent before the study was begun.

5. Results: please explain the elements that have been used in the formula on page 9.

Author: Variables having a p value <0.05 in the univariate analysis were selected and evaluated by multivariate logistic regression models. We then used variables identified by multivariate logistic regression to construct the formula for the predictor model.

Thank you for pointing out this omission. This statement has been added to the previous paragraph (i.e., the paragraph before the formula) to clarify.

6. Discussion: too much of a literature review and lack of reflection on the results.

Author: The Discussion section has been reduced and the introduction of various other predictor models is now in the Introduction section.

7. Conclusion: there is too much of speculations and discussion in the conclusions. Please stay closer to the data/results found.

Author: As shown below, we have re-edit the conclusion to more closely mirror the findings of the study, without editorial comment. Thank you for pointing out this weakness.

**CONCLUSION**

We developed a relatively simple predictor model for survival of more than one week for terminal cancer patients, which is an improvement over existing models. Being able to predict whether death will occur within a week will help facilitate appropriate end-of-life care and increase patient satisfaction. The predictor model developed in this study could be an effective, available index for survival. With fewer
factors in a simple formula, this model could be an important link in the delivery of satisfactory hospice care at end of life.

This prognostic scale, including patient’s cognitive status, edema, performance status, BUN and respiratory rate, showed a relatively high sensitivity and negative predictive value for predicting 7-day survival among terminal cancer patients. We believe that the proposed scale could be useful for predicting survival 7-day for terminal cancer patients, in addition, not late referral to hospice care.

**Discretionary Revisions**

1. Methods. 1st sentence of data collection: "hospitale" admission: do the author mean "hospice" admission?

   Author: The error has been corrected. Thank you!

2. Discussion: it is not clear to me how the prediction model "should improve both quality of life and medical care of terminal patients?"

   Author: This sentence has been changed to: “Correct survival estimations in terminally ill cancer patients help to prevent inappropriate therapies, to avoid action that could worsen the patient’s quality of life, and to get support for patients and families after timely referred to hospice care.”

3. Discussion: next to limitations, the authors could/should also mention the strengths of their study.

   Author: 1. The negative predictive value (NPV) of our prognostic scale is 91.7%, and 90.1% respectively in training, and validation group. This means that our prognostic scale would have more value for identifying those patients not late referral to hospice care than it would have for positively identifying those patients with 7 days to death. 2. To provide a calculator (by R syntax, or by excel) to calculate the probability of survival within 7 days.

   We have integrated this statement after the discussion of the limitations of the study.

**Additional references:**


