Author's response to reviews

Title: Family history of cancer on survival of patients with gastrointestinal cancer in northern Iran, using frailty models

Authors:

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Mahmood Sheikh Fathollahi (mamoosh502002@yahoo.com)

Version: 2 Date: 30 March 2011

Author's response to reviews: see over
Dear van Houwelingen

Enclosed is our article entitled “Family history of cancer on survival of patients with gastrointestinal cancer in northern Iran, using frailty models”.

We revised the manuscript based on the reviewer’s recommendation. We are thankful to the referees and the editor for pointing out some important modification needed in the article. We have thoughtfully taken into account these comments. The explanation of what we have changed in response to the reviewer’s concerns is given point by point. We hope that all this changed fulfill the requirements to make the manuscript acceptable for publication look in forward to hearing from you soon.

Sincerely ghadimi.

On behalf others.

Reviewer's report

Title: Family history of cancer on survival of patients with gastrointestinal cancer in northern Iran, using frailty models

Version: 1 Date: 19 January 2011

Reviewer: Hans C. van Houwelingen

Reviewer's report:
The data could be of interest and worth publishing; however the data-analysis is far from satisfying. Issues to be addressed:

Major

1. Kaplan-Meier estimates of the survival function should be shown, to visualize the data and the effect of important predictors, like gender and family history.

Answer:
Survival Probability

Observed: familyhi = no
Observed: familyhi = yes
Predicted: familyhi = no
Predicted: familyhi = yes

Kaplan-Meier survival estimate
In survival analysis when mortality reaches a peak and then starts to decline, it would be better using a model with a non-monotonic (hump-shaped) failure rate property. Interestingly, both the Log logistic and Log normal own the property. On the other hand, Log logistic dis. has a good approximation for Log normal dis. and so it is preferred to Log normal. Furthermore, Log logistic has a simple form for hazard and survival function and when dealing with censored data it is easier to work with Log logistic than Log normal, and except for in cases of outliers, it reaches a good approximation of Log normal.

The aforementioned pattern for hazard function was the case in our study. Hazard function increased slowly until after a while started to decline. Because of this pattern seen in our data Cox, Weibull, and Exponential models are not appropriate ones and as was said in above Log logistic model seems better as results of our findings verified the issue.

2. The p-values of Table I, compare males and females, I presume. That is not very interesting. I rather had seen the p-values of the log-rank test and hazard ratios derived from simple Cox models for each covariate separately.

Answer:
The table 1 was correct and we dropped out Cox model from our analyses.

3. It does not make sense to compare the partial likelihood of a Cox model with the full likelihood of parametric models. Concluding that the Cox model behaves poorly on the basis of Table II is not correct.
Answer:
According to the fact that the proportionality assumption of Cox model was not met in our data ($p = 0.0014$), using Cox regression was not suitable and so we dropped out Cox model from our analyses.

4. Table III is a bit incomprehensible. First of all, I would rather omit all predictors who do not seem to have an effect at all. Secondly, I expect more than one parameter for categorical covariates with more than two categories like Type and Ethnicity. Thirdly, I have never seen the standardized variability as used here. It is just $1/Z^2$, where $Z$=Wald statistic, I presume. You might as well give the p-values.

Answer:
The table III was correct.
standardized variability dropped out of Table III and added p-values

5. Adding a gamma-frailty term improves the likelihood. That is fine. However, that should be interpreted with care. It shows that the simple model can be improved. Similar improvements could be obtained by adding time-varying effects in the Cox model, as already proposed by Cox in his original paper. The existence of “heterogeneity” can only be concluded if you firmly believe that true model is a simple linear model.

Minor
1. Since all your models have the same number of covariates, you do not need AIC. You can just compare the log-likelihoods.

**Answer:**
The table II was correct and number of covariates dropped out of this table.

2. I do not quite see the usefulness of the deviance residuals plots. They tell the same story as the likelihoods. If you want to give them, they would need some explanation for the clinical readers.

**Answer:**
We added Mean deviance residual to figure I.

**Level of interest:** An article of limited interest
**Quality of written English:** Acceptable
**Statistical review:** Yes, and I have assessed the statistics in my report.
**Declaration of competing interests:**
I declare that I have no competing interests
Referee 2:

Dear Moger

Enclosed is our article entitled “Family history of cancer on survival of patients with gastrointestinal cancer in northern Iran, using frailty models”.

We revised the manuscript based on the reviewer’s recommendation. We are thankful to the referees and the editor for pointing out some important modification needed in the article.

We have thoughtfully taken into account these comments.

The explanation of what we have changed in response to the reviewer’s concerns is given point by point.

We hope that all this changed fulfill the requirements to make the manuscript acceptable for publication look in forward to hearing from you soon.

Sincerely ghadimi.

On behalf others.

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Reviewer's report

Title: Family history of cancer on survival of patients with gastrointestinal cancer in northern Iran, using frailty models

Version: 1 Date: 2 February 2011

Reviewer: Tron Anders Moger

Reviewer's report:

This is a paper which both aims to promote parametric survival models as an alternative to Cox models and introduce frailty models to a wider audience. The main problem with the paper, is that the conclusion that the Cox model fits worse than the parametric models seem to be based on a misunderstanding. One cannot compare log likelihood values (or AIC values which are just functions of the log likelihood values) from parametric models to log partial likelihood values from a Cox model directly to assess the fit of the different models. This argument should be apparent just by using intuition: In the parametric models you use e.g. a Weibull distribution for the baseline hazard. In a Cox model, the baseline hazard would be non-parametric (i.e. more flexible than a parametric distribution). Hence, the Cox model should provide a better fit in all cases except when the baseline hazard is indeed well approximated by a Weibull distribution. In that case, the parametric model may have some interesting additional features compared to the Cox model, which is also the point in the Nardi paper the authors refer to. Another problem is that from the Cox-Snell residual plots, none
of the parametric models appear to have a very good fit (there are departures from the straight line for all parametric models). The deviances come at high values of the Cox-Snell residuals, where there might not be much data, making the deviations less serious, but the authors should respond to this. Also, why not show the Cox-Snell residuals for the Cox model (which should also be possible to get)? Perhaps you will then see that the fit of the Cox model is ok. Due to these problems, consider changing the aim of the paper to just introduce frailty models to the journal's readers. In that case, the main content may still be used, as adding a frailty term to the Cox model seem to significantly improve the fit from the partial log likelihood and AIC values (which should be comparable as you then compare to Cox models where the only difference is that you add a

Answer: 
The figure 2 (Cox-Snell residuals) was correct.

According to the fact that the proportionality assumption of Cox model was not met in our data \( p = 0.0014 \), using Cox regression was not suitable and so we dropped out Cox model from our analyses.

The SAS System
The PHREG Procedure
Model Information

Data Set WORK.PRO
Dependent Variable time_day
Censoring Variable Event_Mortality
Censoring Value(s) 0
Ties Handling BRESLOW

Number of Observations Read 484
Number of Observations Used 484

Summary of the Number of Event and Censored Values

<table>
<thead>
<tr>
<th>Total</th>
<th>Event</th>
<th>Censored</th>
<th>Percent Censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>484</td>
<td>411</td>
<td>73</td>
<td>15.08</td>
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</tbody>
</table>

Linear Hypotheses Testing Results

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<th>Chi-Square</th>
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<tbody>
<tr>
<td>test_proportionality</td>
<td>35.2076</td>
<td>14</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

In survival analysis when mortality reaches a peak and then starts to decline, it would be better using a model with a non-monotonic (hump-shaped) failure rate property. Interestingly, both the Log logistic and Log normal own the property. On the other hand, Log logistic dis. has a good approximation for Log normal dis. and so it is preferred to Log normal. Furthermore, Log logistic has a simple form for hazard and survival function and when dealing with censored data it is easier to work with Log logistic than Log normal, and except for in cases of outliers, it reaches a good approximation of Log normal. 

The aforementioned pattern for hazard function was the case in our study. Hazard function increased slowly until after a while started to decline. Because of this pattern
seen in our data Cox, Weibull, and Exponential models are not appropriate ones and as was said in above Log logistic model seems better as results of our findings verified the issue.

Other comments:
In the methods section you should also describe what to look for in the Cox-Snell and deviance residual plots (as you do when explaining the AIC criterion in the methods section), as many readers might not be familiar with these.
It seems from some of the text in the discussion and in Figure 2 that you are using an accelerated failure time modelling of the covariate effects in the parametric models. But this can’t be correct? When I read table 3, I read it as having a family history of cancer means a 46% increased risk of dying from the standard Cox model, or a 85% higher risk from the exponential model without frailty. An accelerated failure time interpretation would be that an individual with family history of cancer lives 85% longer than a person without cancer.

Answer:
Parametric models is based on log relative hazard form in the table 3. The figure 2 was drown with SAS program.

```
failure _d:  event_mo == 1
analysis time _t:  time_day
```

Iteration 0:  log likelihood = -1107.0722
Iteration 1:  log likelihood = -1056.8598
Iteration 2:  log likelihood = -1048.6838
Iteration 3:  log likelihood = -1048.6399
Iteration 4:  log likelihood = -1048.6399
Exponential regression -- log relative-hazard form

No. of subjects =          484                     Number of obs   =       484
No. of failures =          411
Time at risk    =       443936

LR chi2(18)     =    116.86
Log likelihood  =   -1048.6399                     Prob > chi2     =    0.0000

|                |        Haz. Ratio |      Std. Err. |       z |     P>|z| |      [95% Conf. Interval] |
|----------------|-----------------|---------------|--------|--------|--------------------------|
| age_corr       |   1.005336      |     .0051235  |    1.04 |  0.296 |   [.9953446    1.015429] |
| gender         |   1.123932      |     .1771979  |    0.74 |  0.459 |   [.8251642    1.530874] |
| morg           |   .7600633      |     .1146614  |    -1.82|   0.069 |   [.5655090    1.021551] |
| city_or        |   1.148833      |     .1240132  |    1.29 |  0.199 |   [.9297626    1.41952]  |
| diagnose_2     |   .6419194      |     .1247953  |    -2.28|   0.023 |   [.4385294    .9396417] |
| diagnose_3     |   .3921156      |     .0886615  |    -4.14|   0.000 |   [.2517378    .610773]  |
| cancer         |   .8767501      |     .0918314  |    -1.26|   0.209 |   [.7140364    1.076543] |
| familyhi       |   1.851147      |     .2162521  |    5.27 |  0.000 |   [1.472323    2.327442] |
| educatio       |   .599654       |     .1070598  |    -2.86|   0.004 |   [.4226011    .8508849] |
| mariage        |   1.60927       |     .412205   |    1.86 |  0.063 |   [.9740891    2.658638] |
| drug           |   .9534497      |     .1299687  |    -0.35|   0.727 |   [.7299061    1.245457] |
| cigarett       |   1.349101      |     .1642704  |    2.46 |  0.014 |   [1.062673    1.712731] |
| migratio       |   1.402877      |     .2391909  |    1.99 |  0.047 |   [1.00436    1.95952]   |
| Ijob_2         |   1.062698      |     .4891092  |    0.13 |  0.895 |   [.4311641    2.619252] |
| Ijob_3         |   1.012288      |     .1338136  |    0.09 |  0.926 |   [.7812397    1.311668] |
| Iethnic_2     |   1.357806      |     .4258766  |    0.98 |  0.329 |   [.7342738    2.510831] |
| Iethnic_3     |   1.335815      |     .2274278  |    1.70 |  0.089 |   [.9568106    1.864948] |
| Iethnic_9     |   1.17861       |     .2192558  |    0.88 |  0.377 |   [.8185055    1.697143] |
There are not many typos in the manuscript (Affect instead of effect, page 4, bottom and STAT instead of STATA, page 6, bottom), but many sentences throughout are either incomplete or have strange ordering of words (example: Among the parametric models the Loglogistic model with gamma frailty fitted the data was more appropriate, middle of page 7). The authors should carefully check the manuscript for these sentences.

Answer:
We have revised article and corrected some sentences.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests.
Referee 3:

Dear Katsahian

Enclosed is our article entitled “Family history of cancer on survival of patients with gastrointestinal cancer in northern Iran, using frailty models”.

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Sincerely ghadimi.

On behalf others.

Reviewer’s report

Title: Family history of cancer on survival of patients with gastrointestinal cancer in northern Iran, using frailty models

Version: 1 Date: 1 March 2011

Reviewer: Sandrine Katsahian

Reviewer’s report:
1- Some statistical definition and formula are not given : Major Compulsory Revisions
2- Bibliography and iconography could be better presented: Major Compulsory Revisions

Answer:
According to the fact that the proportionality assumption of Cox model was not met in our data (p = 0.0014), using Cox regression was not suitable and so we dropped out Cox model from our analyses.

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Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being Published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests