Author’s response to reviews

Title: Increased health care utilization by survivors of childhood lymphoblastic leukemia is confined to those treated with cranial or total body irradiation: a case cohort study

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Author’s response to reviews: see over
To BMC Cancer

Dear Editor Dafne Solera and Reviewers,

Thank you very much for the opportunity to revise and resubmit our manuscript entitled “Increased health care utilization of survivors of childhood lymphoblastic leukemia confined to those treated with cranial or total body irradiation: a case cohort study”. We want to thank the reviewers for their thoughtful comments and valuable suggestions.

Again, we think that the revised manuscript is improved, thanks to the reviewer’s comments; our point-by-point responses are listed below. The changes have been entered in the revised manuscript with major changes highlighted.

On behalf of all the authors,

Sincerely,

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Response to reviewers

Reviewer 1

Minor Essential Revisions
1. On page 9 you state "When survivors treated with total body irradiation (TBI) and their controls were excluded, the analyses showed comparable results, illustrating that the observed difference is not explained by an increased number of hospital contacts only among survivors treated with TBI." Do you mean 'the observed difference is explained'? Your conclusion reflects that the difference is driven by the irradiated group.
Response:
Thank you for the valuable comment. This was initially done as a sensitivity analysis, but when we’ve now redone the analyses presented in Table 5 according to Reviewers’ comments, this sentence is confusing and not needed, why it has been excluded in the revised manuscript.

Reviewer 2

Minor and Major Essential Revisions
1. Abstract; Results: You have added the unit “days during study period”. However, we don’t know the length of the study period. Could you either indicate these in the methods section or add it to the unit to give the reader an idea about the absolute burden of these hospital contacts.
Response:
Information about the length of the follow-up has been added to the abstract, in order to clarify this issue.

2. Methods; Paragraph 5: Add the comparison of irradiated and non-irradiated survivors in your aims, because this is a main objective of your article (even stated in the title).
Response:
We presume that the Reviewer means the 5th paragraph of the background section and have added this important piece of information in this paragraph stating the aims of the present study.

3. Methods: Pleas add a paragraph with subtitle where you describe all your exposure variables: which one did you assess, how did you code them, why did you choose selected cut-offs, how do you name them etc. You can take all the description of the exposure variables from the analysis part and move them to this paragraph.
Response:
Changes have been made accordingly in the revised manuscript.

4. Methods, Outcome variables: I would include here the information you wrote at the end of the first paragraph of the statistical analysis where you describe the cut-offs/recoding of your outcome variables. Please argument also shortly, why you chose these cut-offs.
Response:
The sentences concerning the cut-offs have been moved according to the Reviewer’s comment and a sentence describing why these cut-offs were chosen has been added in the revised manuscript.

5. Methods, Statistical analysis, Paragraph 1: At the end of this paragraph, you wrote that you will display continuous variables as median and interquartile range. In effect
you show later median and range. Adapt either of the two things. I would prefer to keep
the range and just delete the word “interquartile”.

Response:
In the first paragraph of the result section the actual range is presented. In the second
paragraph, “rate of hospital contacts”, median and interquartile range is presented. A
sentence clarifying this has been added to the section of statistical analysis.

6. Methods, Statistical analysis, Paragraph 1: Here you have to mention everything you
did for your descriptive analysis, i.e. all the analysis to get the results of Table 1, Table
2, Table 3 and Table 4. Please expand that all your steps are clear to the reader.

Response:
Thank you for this clarifying comment. Changes have been made accordingly in the
revised manuscript.

7. Methods, Statistical analysis, Paragraph 2+3: I still think it is very difficult to follow
exactly what different models you did to investigate your risk factors. I would organize
your analysis steps based on your tables. For Table 5 (to assess the risk of treatment)
you performed 3 multilevel multivariable models, one logistic and two ordinal. State the
outcome and exposure for each model and for what you adjusted additionally. In
addition you did a dose-response analysis for cranial irradiation dose. Here again, how
was cranial irradiation dose exactly included in the model (describe in the paragraph on
exposure variables), for what did you additionally adjust? For Table 6 (to assess socio-
demographic risk factors) you performed again 3 multilevel multivariable models.
Explain again your outcome, exposure and confounding factors you used in each model.

Response:
In the analyses behind the results presented in Table 5, the exposure variables were
case, treatment with chemotherapy only, treatment with cranial irradiation and total
body irradiation. No further adjustments were made. Changes have been made to Table
5 clarifying this. Changes have also been made in the revised manuscript according to
comment regarding analysis of impact of cranial irradiation dose. The analyses of
influence of socio-demographic risk factors on having at least one hospital contact,
number of days in hospital and days in hospital are now described in more detail in the
section of statistics, according to Reviewer’s comment.

8. Results, Rate of hospital contacts: Like for the abstract, state how long the study
period was to give us an impression on the absolute burden.

Response:
The manuscript has been changed according to comment.

9. Results, Rate of hospital contacts: At the end of this paragraph you show results on
an analysis without TBI patients but you never mentioned this in the analysis part or
show any results in the tables. Why did you analyse this only for TBI? How are the
results without cranial irradiated patients? Or without relapsed patients?

Response:
Please see response to comment by Reviewer 1 regarding this (This was initially done
as a sensitivity analysis, but when we’ve now redone the analyses presented in Table 5
according to Reviewers’ comments, this sentence is confusing and not needed, why it
has been excluded in the revised manuscript).

10. Results, Risk factors for hospital contacts: I would divide this paragraph into two
parts. One for the treatment risk factors compared to controls and one on socio-
demographic risk factors comparing survivors and controls.

Response:
Thank you for this valuable comment. Changes have been made in the revised
11. Results, Risk factors for hospital contacts: At the end of paragraph two, you state your results on relapse. I would report these results in the paragraph “rate of hospital contacts”, because it’s only the results from your stratified proportions and you did not really test the risk in a multivariable model.

Response:
As relapse requires considerable increase in treatment and we included the variable in the regression analyses together with treatment modalities, we think it should be reported in the present paragraph. Changes have been made to the section of statistics in the revised manuscript, clarifying this.

12. Results, Risk factors for hospital contacts: You analyse the influence of radiation dose on the hospitalization risk. Why did you not make a real dose-response analysis with the two continuous outcomes? You could show a nice graph if a dose-response relationship really exists. Is this OR you report univariable or have you adjusted for other variables? Please state as that in the results part/methods part.

Response:
Since the two continuous outcome variables “number of hospital contacts” and “number of days in hospital” were so skewed, we chose not to do a real dose-response analysis of these regarding the influence of radiation dose. Changes have been made to the statistics section, describing the analysis performed according to comment.

13. Results, Risk factors for hospital contacts: Please distinguish better in reporting between a) risk factors for hospitalization in survivors and controls, b) differences in risk factors between survivors and controls (interaction term and different directions if present). Was socio-economic status dropped during your backwards model building approach? Or why did you not show this results in your table? Please state what variables you all tested and whether or not they were associated and whether the association differs between survivors and controls.

Response:
We decided a priori not to include the socio-economic parameters in the analyses mentioned, as the income of the parents changed considerably due to inflation and cultural changes during the study period. The distribution of study subjects between the different categories of the highest level of education of the parents and the country of birth of the father was too small for them to be included. A sentence in the revised text now explains this.

14. Discussion, Paragraph 2: For the CCSS and BCCSS you only state relative information (ALL more at risk than others). If available in the literature please state also absolute proportion of hospitalization (like for the Canadian study) and explain possible differences.

Response:
Thank you for this clarifying comment. Changes have been made in the revised manuscript accordingly.

15. Table 5: Report in the title (survivors compared to controls), footnote or table itself what the reference is (controls). Report in the footnote for what other variables this model is adjusted. You have * and # in your table that are not explained in the footnote. I think this should be 2 and 3.

Response:
Changes have been made according to Reviewer’s comment. Please see comment 7. In the revised manuscript, it is stated that no further adjustments were made in the section of statistical analyses.
16. Table 6: As mentioned in the results section, state in the footnote which factors were tested but not included in the final model because not associated. What age did you take for the controls when you have age at diagnosis for the survivors? Please indicate this in the methods part when describing the model and perhaps also in the footnote of the table.

Response:
No other variables then those shown in Table 6 were included in the model. As stated in the paragraph “control cohort” in the methods section, the age of the controls was matched to the age of the survivors.