Reviewer's report

Title: Increased hospitalization of survivors of childhood lymphoblastic leukemia confined to those treated with cranial or total body irradiation: a case cohort study

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Reviewer: Corina S. Rueegg

Reviewer's report:

- Major Compulsory Revisions

The manuscript from Holmqvist and colleagues addresses an interesting and important topic on morbidity and hospitalization after having suffered from ALL during childhood. They have a very high quality dataset to address this question thanks to the unique personal identifier and different registries. Below I have some methodological questions and structural points I hope the authors can overcome to make this important paper ready for publication.

1. Background; Paragraph 4: State your aims more detailed and clearly and address each of your aim in the analysis part and the results part. In the current status it is difficult to follow the results because from the background and analysis part it is not yet clear what you analysed and investigated.

2. Background; Paragraph 4: You aimed to analyse factors for morbidity for health care planning of ALL survivors. While you show the risk factors for morbidity in the results section, you don’t interpret these findings in the discussion regarding your aim on health care planning and implementations into practice.

3. Methods; Outcome variables; Paragraph 1: The Swedish Hospital Register has been a national register only since 1987 and it includes outpatient visits only from 2001 onwards. You also acknowledge this as a limitation in your discussion. Have you done some sensitivity analyses where you include only patients diagnosed later than 5 years prior to 1987 and 2001, respectively? Making such a sensitivity analysis and shortly stating the results might strengthen your paper. If you choose not to make a sensitivity analysis, please state in your limitations section, how this problem could affect your results.

4. Methods; Outcome variables; Paragraph 3: How sure can you be that the increased hospitalizations are not due to routine follow-up visits? Can you give the reader an impression on that? Have you asked some clinicians, what they note in the discharge reports of follow-up visits? If you cannot rule out the possibility that a part of the increased hospitalizations may be due to routine follow-up visits, please acknowledge this in the limitations part of your discussion.

5. Methods; Statistical analyses: Please rewrite this section step by step corresponding to your aims and results. There is no description of the analysis to
compare survivors with and without irradiation and controls. The identification of risk factors for hospitalizations is also not described clearly enough: please describe all the models you performed to get to your results. At the moment it is difficult to follow your results based on the analyses steps given.

6. Methods; Statistical analyses; Paragraph 1: Please explain, why you transformed your outcomes (number of hospitalizations and number of days in hospital) from a continuous to a binary variable. You lose a lot of information by doing this.

7. Methods; Statistical analyses; Paragraph 2: In your analyses on factors associated with your outcomes you write about an ordinal logistic regression for the number of hospital admissions, but the outcome “hospital admissions” was not defined as categorical variable before. The reader does not know how the outcome exactly look like.

8. Methods; Statistical analyses; Paragraph 2: You say that you use random effects for the clusters of cases and controls. Does that mean, that you performed a multilevel logistic regressions? If so, please name it like that at the beginning of the paragraph. If you have done something else, please describe it shortly.

9. Results; Hospitalization rate and diagnoses; Paragraph 1: Show these results additionally stratified for those with cranial irradiation, total body irradiation and not-irradiated patients. Add these numbers in Table 3 or in a separate Table.

10. Results; Risk factors for hospitalization: Show the results for this section in a Table! Show also the adjusted OR for being hospitalized comparing survivors and controls. Distinguish this paragraph between factors associated with hospitalizations overall and differences of risk factors between survivors and controls. Show also the results of interaction terms in your table if you used this to assess differences in risk factors between survivors and controls. Write this paragraph in accordance to the newly written analysis steps.

11. Results; Risk factors for hospitalization; Paragraph 2: You always say that those ALL survivors not treated with irradiation did not show increased hospitalization rates but you never actually show these results. I would re-analyse the data of Table 5 taking only the controls as baseline and showing the risk for non-irradiated ALL survivors, ALL survivors with cranial irradiation and ALL survivors with total body irradiation. Based on these results you can state your conclusion.

12. Discussion; Paragraph 3: You explain the differences in pulmonary diagnoses between your study and references 14 and 16 because of different smoking habits between survivors and controls. But this behaviour would also count for references 14 and 16 and could not explain the difference between them and your study, just the difference within your study.

13. Discussion: Add some clinical implications that might result from your study!
- Minor Essential Revisions

1. Abstract; Results: Add units for the frequency of admissions (3 days per month, days per year?).

2. Abstract; Results: Add the proportion of survivors with total body irradiation as done for those treated with cranial irradiation.

3. Abstract; Results: The conclusion on not difference between non-irradiated ALL survivors and controls was not shown before in the results of the abstract. Please add these results in the abstract or delete this part of the conclusion in the abstract.

4. Background; Paragraph 3: I would focus the background literature more on ALL patients only since this is the population of your paper. Point out more clearly what is known in ALL patients and what are the limitations in the literature making your study important.

5. Results; Hospitalization rate and diagnoses; Paragraph 1: Add units for your numbers of admissions and days in hospital.

6. Discussion; Paragraph 6: You explain conflicting findings regarding risk for hospitalization of males and females because of gender differences in cancer survivors and controls. This sentence is not clear for me.

7. Table 1: Please indicate for each variable whether you used row or column percentages. For example for relapse and cranial irradiation numbers do not sum up to 100%. Please add a column with the total of all survivors and give a p-value for differences between the three populations (chemotherapy only; CRT; TBI)

8. Table 2: Please add a p-value for differences between survivors and controls. The numbers in the two education variables do not add up to 100%.

9. Table 3: Are the number of hospitalizations per year or over the whole period? Please indicate a unit. Are the numbers of days in hospital per each hospitalization or overall? Please add a unit.

- Discretionary Revisions

1. Results; Hospitalization rate and diagnoses: I would split the two topics up with two separate subtitles, one for the hospitalizations and one for the diagnoses.

2. Results; Hospitalization rate and diagnoses; Paragraph 2: You could add some numbers for the diagnoses in this paragraph.

3. Discussion; Paragraph 5: You could add some hypotheses, why the irradiated patients might have higher morbidity regarding the diagnoses you found to be prominent among ALL survivors.

4. Discussion: I would add some strengths of your study!
**Level of interest:** An article of importance in its field

**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