PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Health care utilisation preceding relapse or second malignant neoplasm after childhood acute lymphoblastic leukaemia: a population-based matched cohort study
AUTHORS	Jensen, Karen; Klug Albertsen, Birgitte; Schrøder, Henrik; Zalounina Falborg, Alina; Schmiegelow, Kjeld; Rosthøj, Steen; Callesen, Michael Thude; Vedsted, Peter

VERSION 1 – REVIEW

REVIEWER	Kakaje, Ameer Damascus University Faculty of Medicine, Medical student
REVIEW RETURNED	04-Apr-2021

GENERAL COMMENTS	This study has used valid methods to estimate the use of health care services by children who had ALL and were symptoms-free for 2.5 years and had relapse or other malignancies. Although most of the symptoms can be attributed to the new neoplasm, this study is interesting as this topic was not addressed before and it might be added to future study to modify how these patients are followed-up and therefore I recommend publishing it after considering modifications. Major edit: - Can we mention the reasons why they will visit the health care (increased use of hospital health care services)? (for instance what symptoms?). Because the problem is that the results are probably from the patient having symptoms from the relapse or SMN which justify going to the doctor. Otherwise if they did not go, they would not have been diagnosed with the relapse or SMN in the first place. Another idea is to mention/compare with the study among the adult (reference 25 in this study for instance). - Other things that might be good to match is having other comorbidities (for instance patient in cases groups might have other risk factors/medical or genetic conditions that might have caused this increase in using health care services). - Can we mention which second malignant neoplasms were? - Can we mention (not just in the tables) if the previous response/risk/protocol of ALL affected their current presentation? - If any of the previous points could not be addressed, could you please add them to the limitation section? Minor edits: - Talk a little bit about healthcare system in Denmark; is it for free (to exclude the differences of financial status), is it readily available to everyone? Are there long waiting time? How many times they have routine checkups or/and after being diagnosed with ALL, for how long they are being monitored and how they are treated differently? Will be there major differences with rural and city areas in regards of going to healthcare for check ups And is it mandatory to go for

	healthcare for these children (for instance by the school or primary care to exclude whether having high or low SES might have affected the patterns of going to the healthcare). - It is preferable to use in the abstract the case and reference numbers instead of total patients with ALL (The study included 60 cases and 295 references; 49 (81.7%) of the 60 cases suffered a relapse and 11 (18.3%) an SMN) as it is more relevant. - Just in few words, can we put the definition of first relapse and the protocols for the readers who do not know them? - Is it possible to compare the symptoms/periods of these cases with their symptoms/periods when they were firstly diagnosed? (there might be resemblance or differences that might have affected the results)

REVIEWER	Sharma, Rajesh Delhi Technological University, University School of Management and Entrepreneurship
REVIEW RETURNED	23-Apr-2021

GENERAL COMMENTS	The idea is novel and the manuscript well-written and adheres to its objective. I have a two small suggestions: 1) The discussion of results is short and can be enhanded in reference to implications of the study. (2) Although this may be first Study of this kind fot ALL, are their studies on other leukemia or other neoplasms which can be referred and comparad as to what happens during relapse or SMN of those neoplasia

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

- Can we mention the reasons why they will visit the health care (increased use of hospital health care services)? (for instance what symptoms?). Because the problem is that the results are probably from the patient having symptoms from the relapse or SMN which justify going to the doctor. Otherwise if they did not go, they would not have been diagnosed with the relapse or SMN in the first place. Another idea is to mention/compare with the study among the adult (reference 25 in this study for instance).

Response: Thank you for this relevant question. We agree that increased use of health care in cases before a relapse or an SMN is probably because of symptoms caused by the relapse/SMN. Our objectives were to quantify the amount, duration and sectoral distribution of this increased use of health care. We agree that it would have been of interest to know the reasons for those contacts, but we unfortunately have no available information about this. We have added a sentence to the discussion:

"Another limitation is the absence of information regarding the motivations for contacts to the healthcare system as this information is not available in the National Health Insurance Service Register." (Page 11, lines 10-12)

- Other things that might be good to match is having other comorbidities (for instance patient in cases groups might have other risk factors/medical or genetic conditions that might have caused this increase in using health care services).

Response: Thank you for raising this important point. We have excluded Down Syndrome which is the most common genetic disorder in children developing ALL (Figure 1). We know that survivors of ALL is at risk of late effects. We do not, however, have a systematic register-based registration of these late effects and we are therefore not able to match the amount and type of late affects. We believe that by matching five references to each case minimizes possible confounding from late effects. Further, we believe the increased use of health care before a relapse or an SMN reflects symptoms related to the relapse/SMN. We have added a paragraph to the discussion:

"We had no information on the amount and type of late effects and we were thus not able to match by late effects. However, previous studies suggest that the types of late effects have changed over calendar time making it relevant to match on treatment era (protocol)." (Page 11, lines 17-19)

- Can we mention which second malignant neoplasms were?

Response: We agree with the reviewer that it would have been interesting to report the specific diagnoses. The Danish regulations regarding access to nationwide registries through Statistics Denmark do not allow us to report any variables for a group with less than five individuals to ensure confidentiality. We have added a sentence to the Methods:

"SMN is defined as the occurrence of a new malignant neoplasm. Survivors of ALL are at increased risk of developing a new malignant neoplasm compared to population peers; other haematological malignancies and tumours of the central nerves system are the most common types of SMNs." (Page 6, lines 3-6)

- Can we mention (not just in the tables) if the previous response/risk/protocol of ALL affected their current presentation?

Response: Thank you for this relevant question. We have added a sentence to the discussion:

"However, previous studies suggest that the types of late effects have changed over calendar time making it relevant to match on treatment era (protocol)." (Page 11, lines 18-19)

- If any of the previous points could not be addressed, could you please add them to the limitation section?

Response: Please see above, all previous points are addressed.

- Talk a little bit about healthcare system in Denmark; is it for free (to exclude the differences of financial status), is it readily available to everyone? Are there long waiting time? How many times they have routine checkups or/and after being diagnosed with ALL, for how long they are being monitored and how they are treated differently? Will be there major differences with rural and city areas in regards of going to healthcare for check ups And is it mandatory to go

for healthcare for these children (for instance by the school or primary care to exclude whether having high or low SES might have affected the patterns of going to the healthcare).

Response: Thank you for this relevant question. We have rewritten the paragraph in the methods section for clarification:

"In Denmark, the health care system is tax-financed and free and equally available to all residents (population 5.8 million). All children in Denmark developing ALL are treated in this tax-financed system ensuring that the study is population-based. After ALL treatment cessation, children in Denmark are followed in hospital-based outpatient surveillance programs; visits are scheduled 6-12 times the first year, 4-6 times the second year and 1-3 times a year the following years.19 There are no scheduled visits in general practice." (Pages 4-5, lines 23-3)

- It is preferable to use in the abstract the case and reference numbers instead of total patients with ALL (The study included 60 cases and 295 references; 49 (81.7%) of the 60 cases suffered a relapse and 11 (18.3%) an SMN) as it is more relevant.

Response: Thank you for pointing this out. We agree with the reviewer. To clarify, we have rewritten the relevant parts of the abstract:

"Participants was recruited from a total of 622 childhood ALL 2.5-year event-free survivors diagnosed between 1994 and 2015." (Page 2, lines 7-8)

"Of the 622 childhood ALL survivors, 60 (9.6%) developed a relapse (49) or an SMN (11) and 295 matched references were identified." (Page 2, lines 14-15)

- Just in few words, can we put the definition of first relapse and the protocols for the readers who do not know them?

Response: Thank you for this relevant question. We have clarified that included patients are treated according to three consecutive Nordic Society of Pediatric Hematology and Oncology (NOPHO) trials. It is outside the scope of this study to go into details about the protocols but relevant references are added. A definition of relapse has been included. We have rewritten a part of the Methods:

"Eligible subjects were patients (1.0-17.9 years) diagnosed with non-infant B-cell precursor or T-lineage ALL between 1994 and 2015, and treated according to three consecutive Nordic Society of Pediatric Hematology and Oncology (NOPHO) trials the ALL1992, ALL2000 and ALL2008 trials." (Page 5, lines 9-11)

"A relapse is defined as the reoccurrence of ALL after complete remission; a relapse can occur as an isolated bone marrow relapse, an isolated extramedullary relapse (e.g. the central nervous system or testis) or a combined bone marrow and extramedullary relapse." (Pages 5-6, lines 25-3)

- Is it possible to compare the symptoms/periods of these cases with their symptoms/periods when they were firstly diagnosed? (there might be resemblance or differences that might have affected the results)

Response: Thank you for raising this interesting point. What we know about symptoms at primary diagnosis stems from other register-based studies and we have no information on the specific patients involved in our study. Thus, we are not able to include a comparison between symptoms interval at primary diagnosis and symptoms before relapse/SMN.

Reviewer: 2
The idea is novel and the manuscript well-written and adheres to its objective. I have a two small suggestions:
1) The discussion of results is short and can be enhanded in reference to implications of the study.

Response: Thank you for raising this important point. The present study is based on a small case group and we think a repetition in a bigger population is needed. However, we have added a paragraph to the conclusion to highlight the possible implications:

"If an increased use of general practice services up to 6 months before the diagnosis of a relapse or an SMN is confirmed in future research, there may be a window for earlier diagnosis. An increased knowledge of the patient pathway to relapse/SMN diagnosis is important to ensure optimal organisation of surveillance programmes." (Page 12, lines 19-22)

2) Although this may be first Study of this kind fot ALL, are their studies on other leukemia or other neoplasms which can be referred and comparad as to what happens during relapse or SMN of those neoplasia

Response: Thank you for raising this interesting point. We have systematically looked for publications on the use of healthcare utilisation before relapse/SMN and we did not succeed in finding any studies involving patients with leukaemia. We only found the one study referred to in the text: Rasmussen LA, et al. Healthcare utilisation in general practice and hospitals in the year preceding a diagnosis of cancer recurrence or second primary cancer: a population-based register study. (2019)".

VERSION 2 – REVIEW

REVIEWER	Kakaje, Ameer Damascus University Faculty of Medicine, Medical student
REVIEW RETURNED	26-Jun-2021

GENERAL COMMENTS	Thank you for your work and extensive editing. I believe this paper is ready to be published. Two small edits if it is ok: 1) what are you recommendation when there are an increased visits health care visits (for instance do you recommend doing FBE)? 2) In the abstract, Participants were not "was". Thank you and good luck!

REVIEWER	Sharma, Rajesh Delhi Technological University, University School of Management and Entrepreneurship
REVIEW RETURNED	17-Jun-2021

GENERAL COMMENTS	The authors have sufficiently addressed my comments. The manuscript may be accepted for publication.