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Health care utilisation preceding relapse or second malignant neoplasm after childhood acute lymphoblastic leukaemia: a population-based matched cohort study

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ABSTRACT

Objectives To investigate health care utilisation including both primary and secondary health care 6 months before the diagnosis of a relapse or a second malignant neoplasm (SMN) in survivors of childhood acute lymphoblastic leukaemia (ALL).

Design and setting A Danish population-based matched cohort study linking multiple nationwide registries.

Participants Participants were recruited from a total of 622 childhood ALL 2.5-year event-free survivors diagnosed between 1994 and 2015. Cases were survivors developing a relapse or an SMN and references were survivors still in first remission. Each case was matched with five references on age, sex, treatment protocol and risk group.

Primary outcome measures Consultations in general practice and hospital the last 6 months before relapse or SMN. Cases and references were compared with monthly incidence rate ratios (IRRs) from negative binomial regression models.

Results Of the 622 childhood ALL survivors, 60 (9.6%) developed a relapse (49) or an SMN (11) and 295 matched references were identified. Health care utilisation in general practice increased among cases the last month before the event compared with references with an IRR of 2.71 (95% CI 1.71 to 4.28). Data showed a bimodal structure with a significantly increased number of visits 4, 5 and 6 months before the event. Hospital health care utilisation increased 2 months before the event in cases with an IRR of 5.01 (3.78 to 6.63) the last month before the event and an IRR of 1.94 (1.32 to 2.85) the second-last month comparing cases and references.

Conclusions Survivors of childhood ALL developing a relapse or an SMN have a short period of increased health care utilisation before diagnosis. At hospital, this might be explained by pre-diagnostic examinations. In general practice, data suggest a bimodal structure with children later developing a relapse having more contacts also half a year before the relapse, suggesting that there could be early warnings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The first study to investigate health care utilisation before a relapse or a second malignant neoplasm in survivors of childhood acute lymphoblastic leukaemia.
⇒ Use of complete nationwide registries with nearly no loss to follow-up linked on an individual level ensured that the study was population- based, thus limiting selection bias.
⇒ Outcome data are collected routinely and uniformly in the Danish healthcare system and potential misclassification is thus expected to be non-differential.
⇒ A small case group, leading to low statistical precision.
⇒ Unmeasured confounding could be present.

INTRODUCTION

Five-year survival from childhood acute lymphoblastic leukaemia (ALL) now exceeds 90% with an event-free 5-year survival of around 85%.[1] With increased survival rates, more survivors need scheduled surveillance programmes for detection of possible late effects as well as screening for relapse of ALL or second malignant neoplasm (SMN). ALL survivors are known to have more chronic conditions (late effects) than their general population peers and to have increased use of both primary and secondary health care services after end of treatment.[2–14] Studies examining the occurrence of late effects have contributed with important knowledge to follow-up programmes. However, to the best of our knowledge, no studies have investigated the use of health care before a relapse or an SMN in survivors of childhood ALL.

Studies of health care use before a primary diagnosis of childhood ALL have revealed increased health care use 2–3 months before

the diagnosis, thus reflecting a short period of symptoms.[15 16] Adolescents and young adults are found to have a longer interval with increased primary health care use for 5–6 months before primary diagnosis.[17] Earlier studies indicate that the increased primary health care use could have a bimodal structure with the first peak 10–12 months before the primary diagnosis.[15]

Health care utilisation may reflect both the duration of symptoms before the diagnosis is established and the sectorial distribution of used care associated with these symptoms. Considerable focus is devoted to follow-up strategies for this group, and knowledge about the duration of increased health care use and the sectorial distribution of patients' help-seeking behaviour is therefore highly relevant. To address this knowledge gap, we aimed to analyse health care utilisation in general practice and hospital during the 6-month period preceding a relapse or an SMN in survivors of childhood ALL.

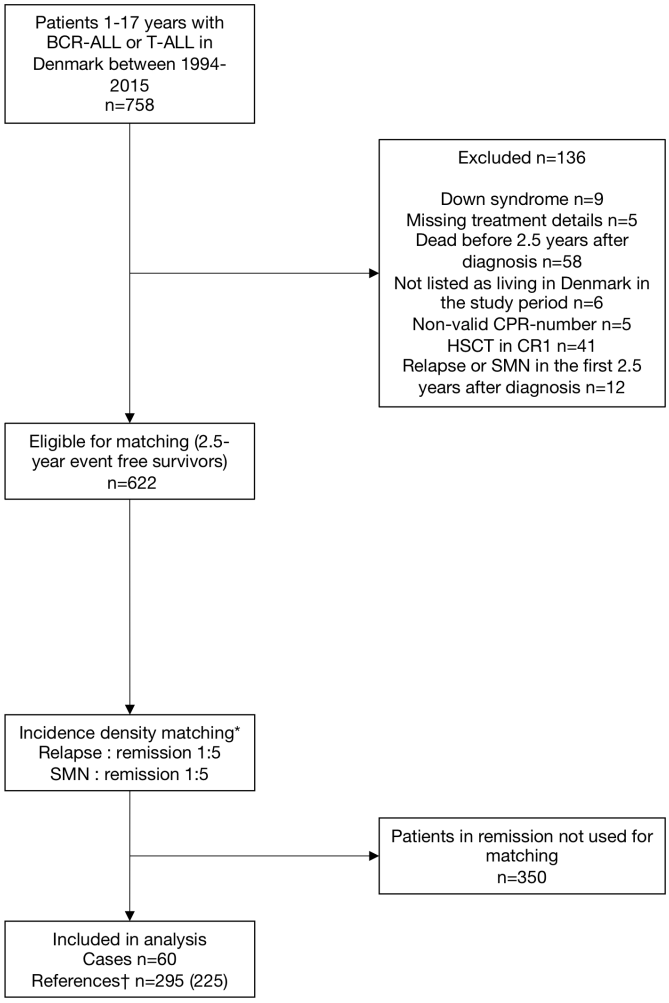

Figure 1 Flow diagram of the study population. Children with relapse/SMN and matched references in first remission. *Matching on age group, sex, risk group and treatment protocol. †The number in brackets is the number of unique persons—the same child can serve as a control more than once and controls can later become cases. BCR-ALL or T-ALL, B-cell precursor or T-lineage acute lymphoblastic leukaemia; CPR number, civil personal registration number; HSCT in CR1, haematopoietic stem cell transplantation in first complete remission; SMN, second malignant neoplasm.

METHODS

Study design and setting

This study is a nationwide, population-based, matched cohort study linking information from several Danish registries. We followed the RECORD guidelines for reporting of studies conducted using observational, routinely collected health data[18] (online supplemental table S1).

In Denmark, the healthcare 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 programmes; 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.

All Danish citizens are assigned a unique identifier, the civil personal registration (CPR) number. The CPR number follows every resident from birth to death; data extracted from Danish public registries were linked on an individual level using the CPR number.

Participants

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.[1 20] Participants were identified in the Danish part of the NOPHO ALL registry. Cases were defined as childhood ALL survivors having a relapse or an SMN as the first event 2.5 years or more after primary diagnosis and before December 2017. Cases were matched 1:5 with childhood ALL survivors still in first remission with the same sex, age group (under 10 years or 10 years or more), NOPHO treatment protocol (ALL1992, ALL2000 or ALL2008) and risk group (high-risk or non-high-risk) (see flow chart, figure 1). Matching was based on incidence density sampling using the Stata command, sttocc. Due to the population-based design, the study sample size was determined by the number of cases in the area during the study period and no sample size calculation was performed.

Data sources and variables

Data were extracted from nationwide registries (table 1) and hosted by Statistics Denmark. Authors had access to a de-identified data output. Data on health care utilisation were extracted for the period 1 January 1997 to 31 December 2017. A relapse is defined as the reoccurrence of ALL after complete remission; a relapse can occur as an isolated bone marrow relapse, an isolated

Table 1 Data sources and variables

	Registries	Variables
Exposures		
	NOPHO ALL Registry*[1 20]	Relapse of ALL First remission
	Danish Cancer Registry†[25]	Second malignant neoplasm
Outcomes		
Primary health care	National Health Insurance Service Register‡[23]	Daytime contacts to general practice: Daytime face-to-face contacts Email consultations Daytime telephone consultations Daytime home visits Out-of-hours contacts: Out-of-hours face-to-face contacts Out-of-hours telephone consultations Out-of-hours home visits Diagnostic procedures in general practice: Blood test Urine test Streptococcus throat test Pulmonary functions test Electrocardiogram
Secondary health care	Danish National Patient Registry§[26]	Contacts to public and private hospitals: Inpatient hospitalisations Outpatient visits
Covariates		
	Danish Civil Registration System[27]	Sex Age Vital status Immigration Emigration
	NOPHO ALL Registry	Diagnosis of childhood ALL Treatment protocol (ALL1992, ALL2000 or ALL2008) Risk group (high-risk or non-high risk) Immunophenotype (B-precursor ALL or T-ALL)

*NOPHO ALL Registry, Nordic Society of Paediatric Haematology and Oncology ALL Registry. The registry holds data on all children aged 1.0–14.9 years in Denmark diagnosed with ALL since 1992. From 2008 and onwards, the ALL Registry was extended to include children and adolescents aged 1.0–17.9 years.
†The Danish Cancer Registry holds information on all new cases of cancer in Denmark.
‡The National Health Insurance Service Register holds information on all contacts to general practice in Denmark. The following contacts were excluded: preventive health examination of children, vaccinations, screening for cervical cancer and pregnancy care. For a complete list of codes, see online supplemental table S2.
§The Danish National Patient Registry holds information on all contacts to public and private hospitals. The following contacts were excluded: visits to the accident and emergency department.
ALL, acute lymphoblastic leukaemia.

extramedullary relapse (eg. the central nervous system or testis) or a combined bone marrow and extramedullary relapse. 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 with population peers; other haematological malignancies and tumours of the central nervous system are the most common types of SMNs.[21]

Statistical methods

The index date was the date of event (relapse or SMN) for cases. The corresponding index date for references was defined as the date with the same interval from the primary diagnosis as for the case. For all included individuals, follow-up started no earlier than 2.5 years after diagnosis to ensure that treatment had ended and remission reached. Health care utilisation was assessed from 6 months before the index date/event.

The monthly rates for primary health care contacts (daytime contacts, out-of-hours contacts and diagnostic procedures) and hospital contacts (inpatient hospitalisations and hospital outpatient contact) were calculated as crude estimates for each of the 6 months preceding the

index date. Negative binominal regression models were used to calculate incidence rate ratios (IRRs) to compare monthly rates of contacts between cases and references. Cluster robust variance estimation was applied to account for possible cluster effects at patient level. This was relevant as measurements on the same person were repeated monthly.

Estimates of IRRs were adjusted for sex, age and time since diagnosis. To adjust for age and time since diagnosis, we used restricted cubic splines with six knots to allow for a non-linear relationship. Furthermore, we performed analyses restricted to cases developing a relapse and to their references. All estimates are presented with 95% CIs. All tests were two-sided and a p value ≤0.05 was considered statistically significant. Data were analysed using the statistical software Stata V.16.1 (StataCorp LLC, College Station, Texas, USA).

Patient and public involvement

The study included no patient and public involvement.

RESULTS

Patient characteristics

The study included 60 cases and 295 references; 49 (81.7%) of the 60 cases suffered a relapse and 11 (18.3%) an SMN (table 2). In two cases, there were fewer than five matching references.

Health care utilisation

We found a mean of 0.73 (95% CI 0.53 to 1.02) daytime general practice visits during the month before the event in cases corresponding to an IRR of 2.71 (95% CI 1.71 to 4.28). For the month before the event, we found an IRR of 8.12 (95% CI 3.01 to 21.86) for general practice out-of-hours contacts and an IRR of 5.89 (95% CI 2.44 to 14.21) for diagnostic procedures in general practice (figure 2). For daytime general practice visits, data suggest a possible bimodal structure with increased IRRs during 4–6 months before the event.

For cases, hospital utilisation was 3.42 (95% CI 2.83 to 4.12) contacts in the last month before the event compared with 0.72 (95% CI 0.61 to 0.85) contacts for references, corresponding to an IRR of 5.01 (95% CI 3.78 to 6.63) the month before the event. For the second-last month before the event, we found an IRR of 1.94 (95% CI 1.32 to 2.85) (figure 3).

In analyses restricted to cases developing a relapse, hospital utilisation also increased 2 months before the event (significantly increased only 1 month before the event). In general practice, data continued to suggest a bimodal structure (figure 4).

Table 2 Characteristics of the study population

Characteristic	Cases* N=60	References† N=295
Sex, n (%)		
Male	38 (63.3)	190 (64.4)
Female	22 (36.7)	105 (35.6)
Median age at index date‡ (IQI)	11.3 (8.4–16.1)	11.1 (7.7–15.7)
Age group at index date, n (%)		
Age <10 years	21 (35.0)	130 (44.1)
Age ≥10 years	39 (65.0)	165 (55.9)
Treatment protocol, n (%)		
NOPHO ALL1992	24 (40.0)	120 (40.7)
NOPHO ALL2000	22 (36.7)	105 (35.6)
NOPHO ALL2008	14 (23.3)	70 (23.7)
Cell line, n (%)		
B-precursor ALL	55 (91.7)	253 (85.8)
T-ALL	5 (8.3)	42 (14.2)
Risk group, n (%)		
Non-high-risk	46 (76.7)	230 (78.0)
High-risk	14 (23.3)	65 (22.0)
Median time from diagnosis to index date (years, IQI)	3.8 (3.2–5.1)	3.8 (3.2–5.1)
Type of event, n (%)		
Relapse	49 (81.7)	–
SMN	11 (18.3)	–

*Cases, survivors of childhood ALL developing a relapse or an SMN as the first event.
†References, survivors of childhood ALL still in first remission matched on age, sex, treatment protocol and risk group.
‡Index date, the date of event for cases and the corresponding date for references.
ALL, acute lymphoblastic leukaemia; IQI, interquartile interval; NOPHO, Nordic Society of Paediatric Haematology and Oncology; SMN, second malignant neoplasm.

DISCUSSION

The present national, population-based matched cohort study shows that utilisation of general practice and hospital services increased significantly 2 months before the diagnosis of a relapse or an SMN compared with references still in first remission. Our data showed a possible bimodal structure for daytime consultations in general practice in general and for cases developing a relapse more pronounced, with increased utilisation 5–6 months before relapse. This indicates that there could be early warnings. The increased use of hospital health care services the last month before relapse is most likely explained by the diagnostic workup.

Strengths and limitations

The population-based design with use of nationwide registries linked on an individual level is a strength. This ensured optimal completeness of data and follow-up. However, a relapse diagnosis is not

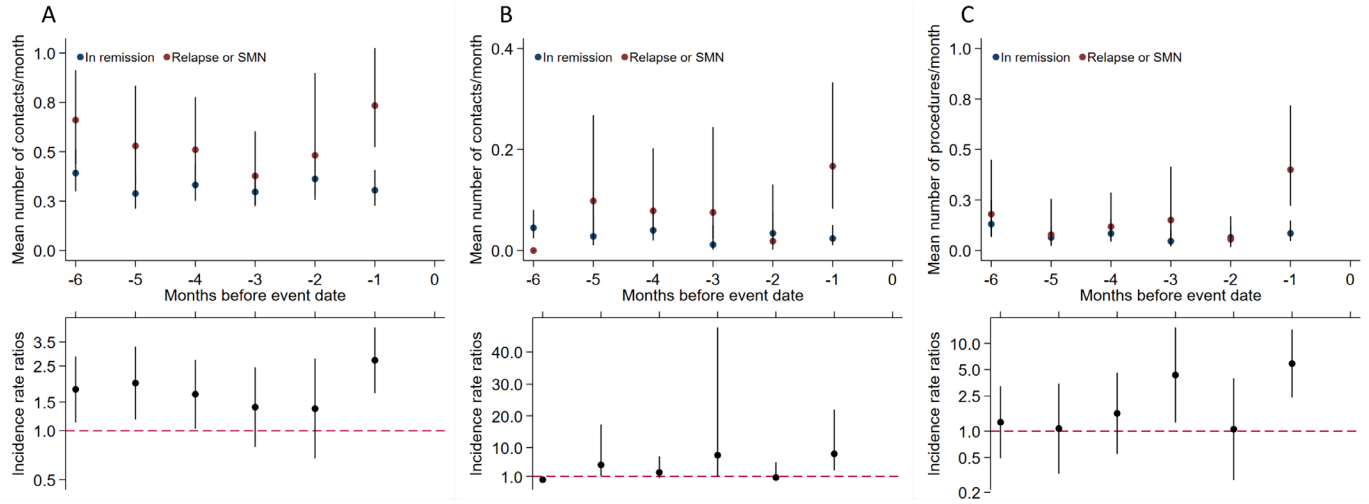

Figure 2 General practice health care utilisation. General practice utilisation by months before event for cases* (n=60) compared with references† (n=295). (A) Daytime. (B) Out-of-hours. (C) Diagnostic procedures. Top panel: contacts/diagnostic procedure mean rates per month presented as crude rates. Bottom panel: incidence rate ratios adjusted for age, sex and time since diagnosis. Vertical lines represent 95% CIs. *Cases, survivors of childhood ALL developing a relapse or an SMN as the first event. †References, survivors of childhood ALL still in first remission matched on age, sex, treatment protocol and risk group. ALL, acute lymphoblastic leukaemia; SNM, second malignant neoplasm.

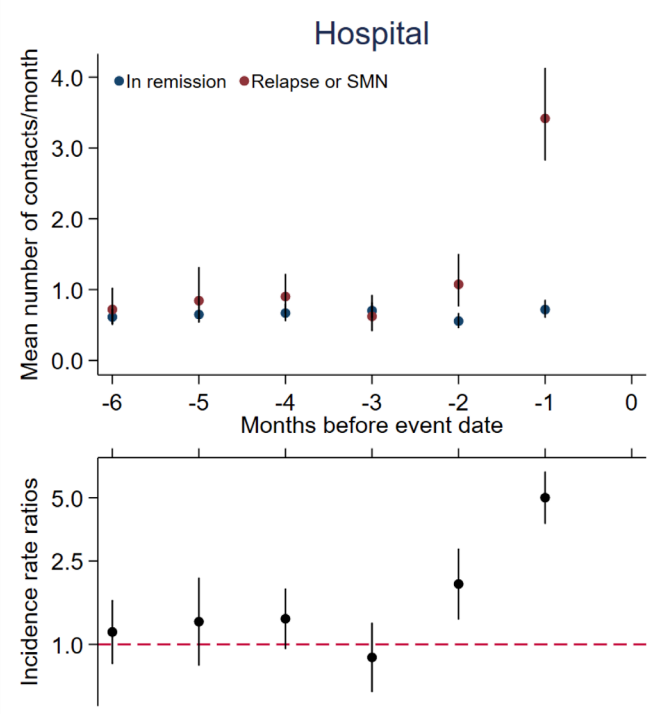

Figure 3 Hospital health care utilisation. Hospital health care utilisation by months before event for cases* (n=60) compared with references† (n=295). Top panel: contacts mean rates per month presented as crude rates. Bottom panel: incidence rate ratios adjusted for age, sex and time since diagnosis. Vertical lines represent 95% CIs. *Cases, survivors of childhood ALL developing a relapse or an SMN as the first event. †References, survivors of childhood ALL still in first remission matched on age, sex, treatment protocol and risk group. ALL, acute lymphoblastic leukaemia; SMN, second malignant neoplasm.

registered in the Danish Cancer Registry. Therefore, data on relapses were collected from the NOPHO ALL registry.[1 20] The NOPHO ALL registry is a very robust data source as it is updated regularly by research nurses and paediatric oncologists. Nevertheless, the registry might not contain data on all relapses that occur after patients leave a paediatric department. Children with a relapse that was unregistered would belong to the reference group, which could lead to bias towards underestimating relapse frequency and the differences in use of health care services.

Electronic outcome data are collected routinely and uniformly in the Danish healthcare system. Data were collected for remuneration and not for the purpose of the present study. Potential misclassification of outcomes is expected to be equally distributed among cases and references, and any such misclassification is expected to be non-differential.[22]

The relatively small case group in our study is a limitation, leading to a low statistical precision with broad CIs. 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.[23]

We compared periods with the same interval from diagnosis in cases and references as previous research has shown that time since diagnosis affects utilisation of health care.[8 9] We made an effort to reduce confounding by age, gender, calendar period and treatment regime by matching cases with references. 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

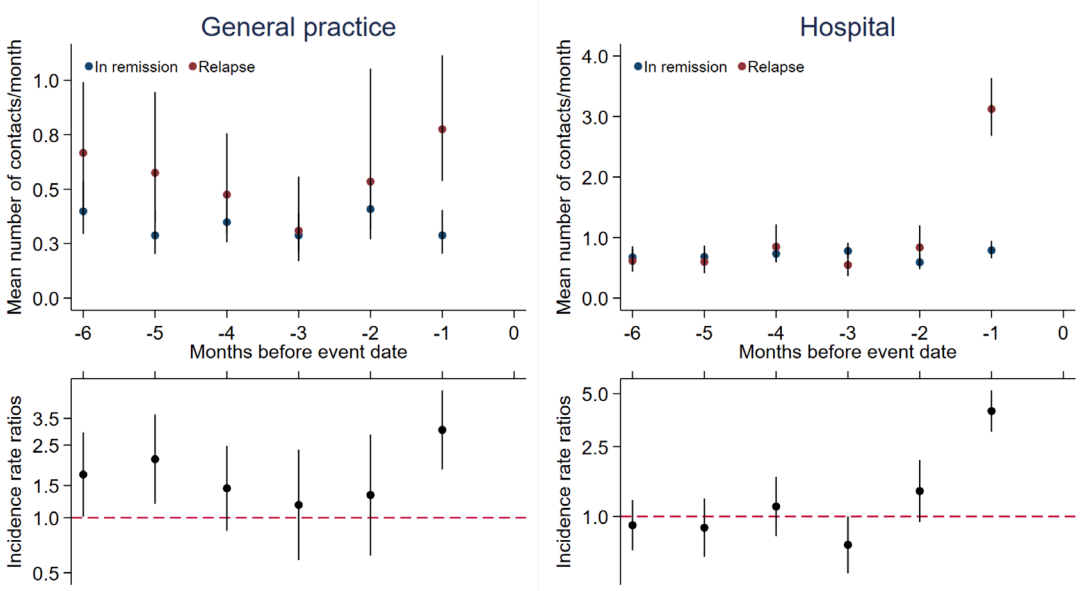

Figure 4 Health care utilisation by months before event for cases (n=49) compared with references* (n=243). Cases are survivors of childhood ALL developing a relapse as the first event (cases developing an SMN are excluded in this analysis). Top panel: contacts mean rates per month presented as crude rates. Bottom panel: incidence rate ratios adjusted for age, sex and time since diagnosis. Vertical lines represent 95% CIs. *References, survivors of childhood ALL still in first remission matched on age, sex, treatment protocol and risk group. ALL, acute lymphoblastic leukaemia; SMN, second malignant neoplasm.

time making it relevant to match on treatment era (protocol).[6]

We were not able to adjust for sociodemographic factors and unmeasured confounding could thus be present. We expect potential bias to be negligible, and we believe that our findings can be generalised to other countries with comparable healthcare systems.

Comparison with existing literature

Previous studies on health care utilisation in ALL survivors have found increased use of primary and secondary health care after end of treatment.[2–14] However, previous studies did not evaluate health care use before a relapse or an SMN. Studies on health care utilisation before primary ALL diagnosis in childhood found increased use of health care 2–3 months before the primary diagnosis[15 16]; and based on these findings, we expected a short duration of increased health care use. Furthermore, a bimodal structure for general practice health care use before the primary diagnosis is reported, but with the first peak 10–12 months before diagnosis.[15]

A recent study examining use of health care before a cancer recurrence or an SMN in adult cancer survivors reported increased use of health care up to a year before diagnosis among patients diagnosed with a wide range of solid tumours.[24] Based on knowledge on health care use before a primary cancer, it is expected that patients with solid tumours have a longer interval of increased health care utilisation.[15 17]

Conclusions

Survivors of childhood ALL developing a relapse or an SMN when in remission had a higher use of general practice and hospital health care services compared with matched references, 1–2 months before the event. There was a possible bimodal structure for daytime visits to general practice with increased visits also 4–6 months before the event. As health care utilisation may be seen as a proxy for morbidity, this indicates that there could be early warnings. To the best of our knowledge, this is the first study to investigate use of health care before a relapse or an SMN in survivors of childhood ALL in remission, and further research is needed. 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.

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Contributors KSJ designed the study, analysed and interpreted data and wrote the manuscript; BKA interpreted data and edited the manuscript; HS designed the study and edited the manuscript; AZF analysed and interpreted data and edited the manuscript; KS interpreted data and edited the manuscript; SR interpreted

data and edited the manuscript; MTC interpreted data and edited the manuscript; PV designed the study, interpreted data and edited the manuscript. All authors approved the final manuscript.

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Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

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