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Article

Long-Term Risk of Hospitalization for Somatic Diseases Among Survivors of Childhood Acute Lymphoblastic Leukemia

Gitte Vrelits Sørensen, PhD [1,2,*] Vanna Albieri, PhD,[3] Anna Sällfors Holmqvist, PhD,[4] Friederike Erdmann, PhD,[5,6] Hanna Mogensen, MSc,[7] Mats Talbäck, PhD,[7] Marianne Ifversen, PhD,[8] Timothy Lee Lash, DSc,[9] Maria Feychting, PhD,[7] Kjeld Schmiegelow, DMSc [8,10] Mats Marshall Heyman, MD,[11] Jeanette Falck Winther, DMSc,[2,5] Henrik Hasle, PhD [1]

[1]Department of Pediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Clinical Medicine, Faculty of Health, Aarhus University and University Hospital, Aarhus, Denmark; [3]Unit of Statistics and Data Analysis, Danish Cancer Society Research Center, Copenhagen, Denmark; [4]Department of Clinical Sciences, Lund University, Pediatric Oncology and Hematology, Skåne University Hospital, Lund, Sweden; [5]Childhood Cancer Research Group, Danish Cancer Society Research Center, Copenhagen, Denmark; [6]Division of Childhood Cancer Epidemiology, Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; [7]Unit of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [8]Department of Pediatrics and Adolescent Medicine, Copenhagen University Hospital, Copenhagen, Denmark; [9]Department of Epidemiology, Rollins School of Public Health, and Winship Cancer Institute, Emory University, Atlanta, GA, USA; [10]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; and [11]Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

[*]**Correspondence to:** Gitte Vrelits Sørensen, PhD, Pediatrics and Adolescent Medicine, Aarhus University Hospital, Palle Juul-Jensens Blvd 99, 8200 Aarhus N, Denmark (e-mail: gitte@clin.au.dk).

Abstract

Background: Survivors of childhood acute lymphoblastic leukemia (ALL) may be at increased long-term risk of hospitalization for somatic diseases. However, large population-based cohort studies with risk estimates for survivors successfully cured without experiencing a relapse or requiring hematopoietic stem cell transplantation (HSCT) are lacking. **Methods:** Danish and Swedish patients diagnosed with ALL before age 20 years in 1982-2008 were identified in the national cancer registries. Five-year survivors and matched population comparisons without childhood cancer were followed for hospitalization for 120 somatic disease categories in the national hospital registries from 5 years postdiagnosis until 2017, and disease-specific hospitalization rate ratios (RR) were calculated. The mean cumulative count method was used to estimate the mean number of multiple and recurrent disease-specific hospitalizations per individual. **Results:** A total of 2024 5-year survivors and 9797 population comparisons were included. The overall hospitalization rate was more than twice as high compared with comparisons (RR = 2.30, 95% confidence interval [CI] = 2.09 to 2.52). At 30 years postdiagnosis, the mean cumulative hospitalization count was 1.69 (95% CI = 1.47 to 1.90) per survivor and 0.80 (95% CI = 0.73 to 0.86) per comparison. In the subcohort without relapse or HSCT (n = 1709), the RR was 1.41 (95% CI = 1.27 to 1.58). **Conclusions:** Survivors of childhood ALL were at increased long-term risk for disease-specific hospitalizations; however, in survivors without relapse or HSCT, the rate was only modestly higher than in population comparisons without a childhood cancer. The absolute mean numbers of multiple and recurrent hospitalizations were generally low.

Childhood acute lymphoblastic leukemia (ALL) survivors are at risk of a wide range of late effects. During the past half-century, survival among childhood ALL patients has increased impressively, resulting in 5-year survival rates exceeding 90% (1-4). Unfortunately, there may be consequences of childhood ALL, and adverse effects may persist or become evident many years after end of therapy (5,6). Late effects include second malignant neoplasms (SMN); cardiovascular, endocrine, pulmonary, neurological, musculoskeletal, and cognitive complications as documented by clinically based assessments; self-reported chronic health conditions; and excess risk of hospitalization (5-12). However, previous studies lacked clinical information about the leukemia type or treatment (11,13), and other studies were limited by potential selection bias and risk of recall bias in questionnaire studies (5-7,12) or small sample size (14,15). Survivors who were successfully cured without experiencing a relapse or

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receiving a hematopoietic stem cell transplantation (HSCT) are less heavily treated and may have a different risk and pattern of late disease-specific hospitalizations. However, large long-term follow-up population-based studies with separate hospitalization estimates for this subgroup of ALL survivors are lacking in the literature (16).

In this population-based cohort study on 5-year survivors of childhood ALL, diagnosed 1982-2008 in Denmark and Sweden, we evaluated the long-term risk of hospitalization for 120 somatic disease-specific categories. Unique data for subgroups of ALL survivors, based on risk groups, relapse, and HSCT status, were included, and the magnitude of the hospitalization burden was investigated by considering both multiple and recurrent hospitalizations.

Methods

Study Design Overview

The cohort of ALL survivors is a subset of the original Nordic population-based research program Adult Life after Childhood Cancer in Scandinavia described earlier (11,17). The Socioeconomic consequences in Adult Life after Childhood Cancer in Scandinavia (SALiCCS) program builds on data from the Adult Life after Childhood Cancer in Scandinavia cohort, including updated hospitalization outcomes with follow-up until 2017, and with the possibility to link to treatment data from the Nordic Society of Paediatric Haematology and Oncology (NOPHO) (18).

Study Setting

Denmark and Sweden offer tax-supported public health care. Both countries have a civil registration system with national administrative registries, and the unique personal identification number assigned to all inhabitants allows for accurate individual-level linkage of information between registries (19,20). Information on vital status and emigration during follow-up was obtained from the national population registries, with virtually no loss to follow-up (21). The population-based national cancer registries were used to obtain information on type of cancer and date of cancer diagnosis (22).

The NOPHO ALL database includes data on patient characteristics, for example, immunophenotype, risk stratification, and treatment information, including HSCT and relapse data (23,24). The registration from Denmark initially included only patients diagnosed with ALL before age 15 years; however, in Sweden, patients aged 15-17 years were systematically registered since the early 1980s. During the 1980s, standard risk (SR) and intermediate risk (IR) patients were treated according to NOPHO protocols, whereas high-risk (HR) patients were treated on regional or national protocols. Since January 1992, all patients with childhood ALL in the Nordic countries have been treated on common NOPHO protocols (23).

Study Population

From the SALiCCS cohort, we identified all patients diagnosed with a primary diagnosis of ALL in the national cancer registries before the age of 20 years between January 1, 1982, and June 30, 2008 (n = 2819) (Figure 1). For each ALL patient, 5 individually matched comparisons were randomly selected from the general population among those who were alive on the date of the cancer diagnosis of the corresponding patient (index date), of the same sex, age (calendar year of birth), and country (Denmark) or municipality (Sweden) of residence, and without a cancer diagnosis before the age of 20 years (n = 14 024). We linked the ALL patients to the clinical data in the NOPHO database. A total of 228 patients were not found in the NOPHO database and were excluded (78% of these were aged >15 years at ALL diagnosis). We also excluded patients with mature B-cell ALL (n = 36), patients younger than 12 months at diagnosis (n = 71), those with Philadelphia chromosome–positive ALL treated with tyrosine kinase inhibitors (n = 11), as well as patients diagnosed after 1991 but not treated according to the common NOPHO ALL-92 or NOPHO ALL-2000 protocols (n = 39). We also excluded ALL patients (n = 57) and matched comparisons (n = 5) with Down syndrome (International Classification of Diseases 8th revision [ICD-8]: 759.3, ICD-9: 758.0, ICD-10: Q-90), because this condition may confound associations between ALL and several of the outcomes. Results for these patients have been reported separately (25). In addition, we excluded patients and matched comparisons with less than 5-year survival from the index date (n = 353 and n = 318, respectively). When excluding ALL patients, their corresponding matched comparisons were also excluded. Thus, the study cohort included a total of 2024 5-year survivors of noninfant, childhood ALL and 9797 matched population comparisons without childhood cancer.

Furthermore, we defined a nonrelapse or non-HSCT subcohort by excluding 5-year survivors with a relapse before 5-year survival date or treatment with HSCT in first complete remission (n = 315) and censored participants at the time of relapse if the relapse occurred after the 5-year survival date. The subcohort included a total of 1709 5-year survivors and 8272 matched population comparisons without childhood cancer (Figure 1).

Hospital Contacts

The national hospital registries collect information on virtually all hospital admissions and have been described in detail previously (26,27). Survivors of ALL and comparisons were linked to the national hospital registries, and a full in-patient hospital admission history was established for each person from the 5-year survival date. Only the primary diagnosis for each hospital admission was included. We grouped the somatic hospital diagnoses into 120 disease-specific categories, which in turn were assembled into 12 main diagnostic groups (Supplementary Table 1, available online). Diagnostic categories of ICD-9 and ICD-10 were adapted to ICD-8 as previously done (11). Psychiatric hospitalizations will be reported in a separate study. We also did not include the ICD sections on symptoms and ill-defined conditions, injuries, violence and accident, congenital malformations, childbirth, or pregnancy-related complications. Information on SMN among ALL survivors and first primary cancers among comparisons was obtained from the national cancer registries.

Our main outcome was overall hospitalization, defined as first-time inpatient hospitalization for each of the 120 specific disease categories. This was evaluated overall and within each of the 12 main diagnostic groups. As a secondary outcome, we investigated the mean cumulative count (total burden) of all disease-specific inpatient hospitalizations. This was defined as overall hospitalization but also including readmissions for non-cancer disease categories.

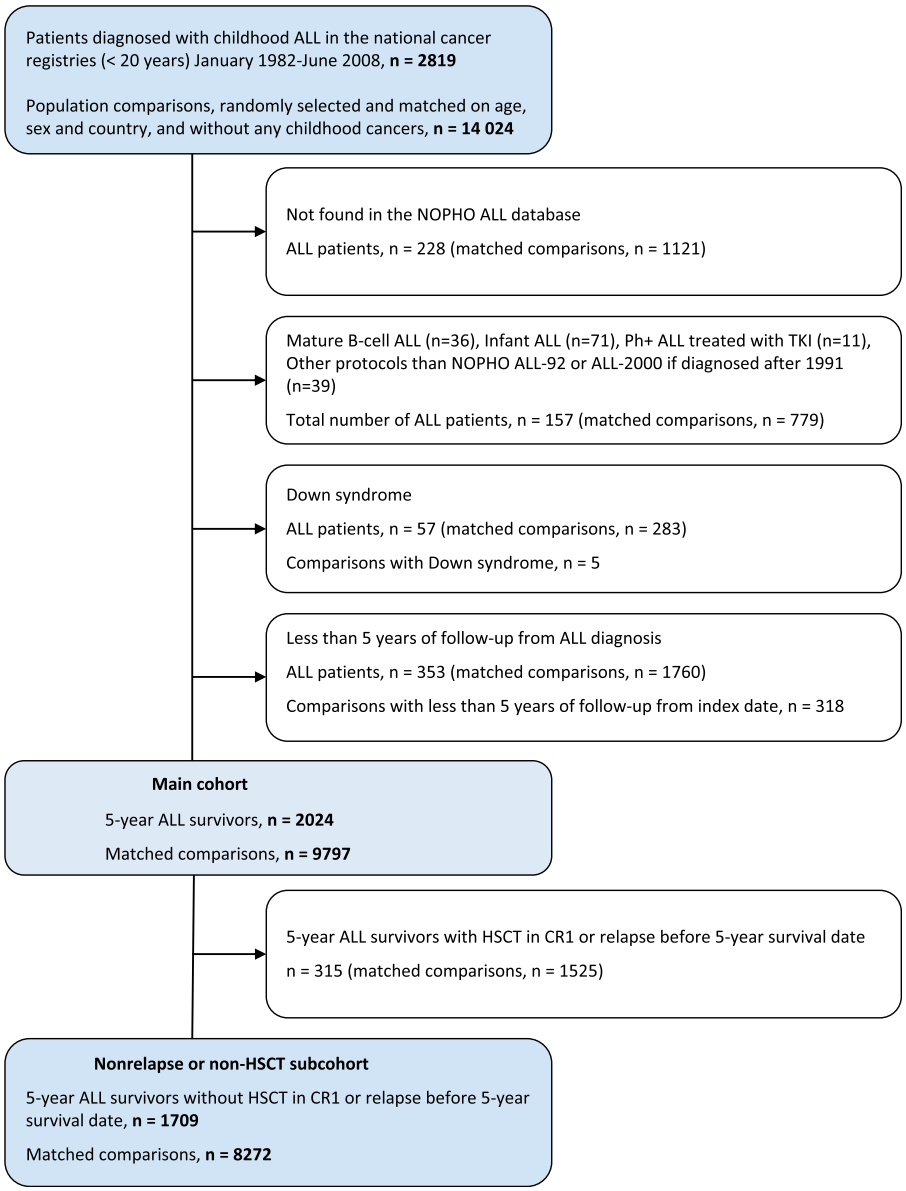


Figure 1. Flowchart showing exclusions from the study cohorts. The exclusion step "other protocol than NOPHO ALL-92 or NOPHO ALL-2000 if diagnosed after 1991" excludes primarily patients treated according to the subsequent Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL-2008 protocol before official opening of the protocol. ALL = acute lymphoblastic leukemia; CR1 = first complete remission; HSCT = hematopoietic stem cell transplantation; TKI = Tyrosine kinase inhibitor; Ph+ = Philadelphia chromosome positive.

Outpatient and emergency department contacts have been included in the national hospital registries since 1995 in Denmark and since 2001 in Sweden (26,27). To investigate the effect of also including outpatient hospitalization in our main outcome, we defined a restricted cohort with full history of outpatient hospital contacts from the 5-year survival date. In this cohort, we investigated overall hospitalization (our main study outcome) and overall hospitalization when outpatient hospital contacts were also included.

Definition of Clinical Variables

From the NOPHO database, we obtained information on immunophenotype, cytogenetic aberration, risk stratification, relapse date, HSCT date, and assigned treatment protocol (23,24,28). We defined the following treatment protocol periods as nonuniform protocol period 1 (January 1982-June 1986), nonuniform protocol period 2 (July 1986-December 1991), NOPHO ALL-92 protocol (January 1992-September 2001), and NOPHO ALL-2000 protocol (January 2002-June 2008). Risk stratification was grouped as SR, IR, and HR, and the HR group also included very HR and extra HR groups from the NOPHO ALL-92 and NOPHO ALL-2000 protocol (Supplementary Table 2, available online). For survivors diagnosed before July 1986 (n = 267), we lacked information on cranial irradiation, and therefore these survivors and their matched comparisons were omitted from analyses involving cranial irradiation. For survivors diagnosed July 1986 to December 1991, we used the assigned protocol as proxy for irradiation on an intention-to-treat basis. For survivors diagnosed after 1991, information on cranial irradiation was available in the NOPHO database.

Table 1. Characteristics of 5-year survivors of childhood ALL and matched population comparisons without childhood cancer

Characteristics	Main cohort		Subcohort	
	ALL survivors	Matched comparisons	Nonrelapse or non-HSCT ALL survivors	Matched comparisons
Overall, No. (%)	2024 (100)	9797 (100)	1709 (100)	8272 (100)
Sex, No. (%)				
Male	1117 (55.2)	5400 (55.1)	922 (53.9)	4455 (53.9)
Female	907 (44.8)	4397 (44.9)	787 (46.1)	3817 (46.1)
Country, No. (%)				
Denmark	730 (36.1)	3469 (35.4)	623 (36.5)	2964 (35.8)
Sweden	1294 (63.9)	6328 (64.6)	1086 (63.5)	5308 (64.2)
Age at end of follow-up, No. (%)				
6-14 y	185 (9.1)	728 (7.4)	169 (9.9)	660 (8.0)
15-24 y	792 (39.1)	3755 (38.3)	665 (38.9)	3241 (39.2)
25-34 y	719 (35.5)	3639 (37.1)	610 (35.7)	3072 (37.1)
35-49 y	328 (16.2)	1675 (17.1)	265 (15.5)	1299 (15.7)
Censoring event, No. (%)				
End of study follow-up	1828 (90.3)	9138 (93.3)	1556 (91.0)	7724 (93.4)
Emigration	82 (4.1)	614 (6.3)	70 (4.1)	510 (6.2)
Death	114 (5.6)	45 (0.5)	16 (0.9)	38 (0.5)
Relapse after 5-y survival date[a]	—	—	67 (3.9)	(0.0)
Median y of follow-up from diagnosis, No. (IQR)	20 (14-26)	20 (14-26)	20 (14-26)	19 (14-26)
Calendar time-period of index date, No. (%)				
1982-1991	651 (32.2)	3130 (31.9)	523 (30.6)	2514 (30.4)
1992-2001	853 (42.1)	4127 (42.1)	738 (43.2)	3567 (43.1)
2002-2008	520 (25.7)	2540 (25.9)	448 (26.2)	2191 (26.5)
Age at leukemia diagnosis, No. (%)				
1-4 y	1099 (54.3)	—	957 (56.0)	—
5-9 y	540 (26.7)	—	449 (26.3)	—
10-14 y	310 (15.3)	—	242 (14.2)	—
15-18 y	75 (3.7)	—	61 (3.6)	—
Immunophenotype, No. (%)				
B-ALL	1802 (89.0)	—	1542 (90.2)	—
T-ALL	188 (9.3)	—	144 (8.4)	—
Missing	34 (1.7)	—	23 (1.3)	—
Cytogenetic aberration, No. (%)				
Normal	401 (19.8)	—	348 (20.4)	—
Hyperdiploid (>50 chromosomes)	466 (23.0)	—	414 (24.2)	—
t(12; 21)(p13; q22)/*ETV6-RUNX1*	221 (10.9)	—	196 (11.5)	—
Other aberrations	399 (19.7)	—	313 (18.3)	—
Missing cytogenetic data	537 (26.5)	—	438 (25.6)	—
Risk stratification, No. (%)				
Standard	766 (37.8)	—	679 (39.7)	—
Intermediate	739 (36.5)	—	631 (36.9)	—
High	519 (25.6)	—	399 (23.3)	—
Treatment protocol (time period), No. (%)				
Period 1 (1982-1986)	267 (13.2)	—	199 (11.6)	—
Period 2 (1986-1991)	384 (19.0)	—	324 (19.0)	—
NOPHO ALL-92 (1992-2001)	809 (40.0)	—	704 (41.2)	—
NOPHO ALL-2000 (2002-2008)	564 (27.9)	—	482 (28.2)	—
HSCT, No. (%)				
HSCT in CR1	65 (3.2)	—	0 (0)	—
HSCT after relapse	198 (9.7)	—	0 (0)	—
No HSCT in CR1 or after relapse of ALL	1761 (87.1)	—	1709 (0)	—
Relapse, No. (%)				
Yes: 1st relapse before 5-y survival date	256 (12.6)	—	0 (0)	—
Yes: 1st relapse after 5-y survival date[a]	67 (3.3)	—	67 (3.9)	—
No[b]	1701 (84.0)	—	1642 (96.1)	—

(continued)

Table 1. (continued)

Characteristics	Main cohort		Subcohort	
	ALL survivors	Matched comparisons	Nonrelapse or non-HSCT ALL survivors	Matched comparisons
Cranial irradiation[c], No. (%)				
Yes	304 (17.3)	—	256 (17.0)	—
No	1438 (81.8)	—	1242 (82.3)	—
Missing	15 (0.9)	—	12 (0.8)	—

[a]The nonrelapse or non-HSCT subcohort was censored at relapse after 5-year survival date. ALL = acute lymphoblastic leukemia; CR1 = first complete remission; HSCT = hematopoietic stem cell transplantation; NOPHO = Nordic Society of Paediatric Haematology and Oncology.
[b]No relapse before 5-year survival date or during follow-up.
[c]Only in the restricted cohort diagnosed after June 30, 1986, because cranial irradiation information was not available on an individual basis for survivors diagnosed before July 1986 (n = 267).

Table 2. Overall hospitalization rate ratio among 5-year survivors of childhood ALL relative to matched population comparisons without childhood cancer

Survivor characteristics	Main cohort ALL survivors (n = 2024)			Subcohort Nonrelapse or non-HSCT ALL survivors (n = 1709)		
	Person-years at risk	No. of disease-specific hospitalizations[a]	RR[b] (95% CI)	Person-years at risk	No. of disease-specific hospitalizations[a]	RR[b] (95% CI)
Total	30 391	1491	2.30 (2.09 to 2.52)	25 595	787	1.41 (1.27 to 1.58)
Sex						
Male	16 442	735	2.33 (2.05 to 2.66)	13 477	369	1.41 (1.18 to 1.67)
Female	13 950	756	2.26 (1.98 to 2.58)	12 118	418	1.42 (1.23 to 1.64)
Type of ALL						
B-ALL	27 049	1290	2.24 (2.03 to 2.48)	23 053	683	1.36 (1.22 to 1.53)
T-ALL	2649	134	2.31 (1.80 to 2.95)	2073	72	1.56 (1.15 to 2.12)
Risk stratification						
Standard	12 010	500	1.96 (1.68 to 2.30)	10 325	283	1.27 (1.04 to 1.55)
Intermediate	10 870	569	2.45 (2.12 to 2.82)	9248	292	1.45 (1.24 to 1.69)
High	7511	422	2.61 (2.24 to 3.02)	6021	212	1.59 (1.32 to 1.92)
Cranial irradiation[c]						
No	18 179	855	2.28 (2.02 to 2.57)	15 708	461	1.41 (1.22 to 1.62)
Yes	5519	277	2.46 (2.04 to 2.97)	4767	162	1.62 (1.31 to 1.99)
Time since index date, y						
5-9	9812	669	3.70 (3.24 to 4.23)	8281	302	1.96 (1.66 to 2.32)
10-19	14 048	535	1.75 (1.53 to 2.00)	11 897	322	1.21 (1.04 to 1.41)
≥20	6531	287	1.78 (1.48 to 2.13)	8281	163	1.19 (0.96 to 1.46)

[a]First-time hospitalization among ALL survivors for a selected set of medical conditions (120 disease categories); each person may be hospitalized for more than 1 specific disease category. ALL = acute lymphoblastic leukemia; CI = confidence interval; HSCT = hematopoietic stem cell transplantation; RR = rate ratio.
[b]Adjusted for sex, year of birth, country, and calendar time period of diagnosis or index date.
[c]Survivors diagnosed before July 1986 (n = 267) were omitted from the cranial irradiation exposure analysis because of missing exposure data.

Statistical Analyses

Analyses were performed separately for the entire cohort and for the subcohort without HSCT or relapse. Follow-up for hospitalizations started 5 years after the date of ALL diagnosis for survivors and 5 years after index date for population comparisons. Follow-up ended on date of death, emigration, or end of the study period (Denmark: July 10, 2017; Sweden: December 31, 2016), whichever occurred first.

Overall hospitalization rate ratios (RRs) and 95% confidence intervals (CIs), considering first-time inpatient hospitalization for each of the 120 specific disease categories, were calculated in repeated event marginal rates models (29). Considering that some individuals have several different first-time hospitalizations during follow-up, a sandwich estimator was used to compute a robust variance for the models. The analyses were adjusted for sex, year of birth, country, and calendar period of diagnosis or index date (1982-1991, 1992-2001, and 2002-2008). To make the best possible adjustment for age, we used age as the underlying timescale (30). For the overall hospitalization outcome, we separately analyzed the effect of sex, type of ALL (B-cell ALL, T-cell ALL), risk stratification (SR, IR, HR), and cranial irradiation (yes or no). The rate of first-time disease-specific hospitalization was analyzed within each time period of follow-up (5-9, 10-19, +20 years) without counting readmissions for the same disease-specific hospitalization in subsequent time periods of follow-up.

To illustrate risk on an absolute scale, we estimated the cumulative incidence of first hospitalization for any disease over time, taking the competing event of death into account.

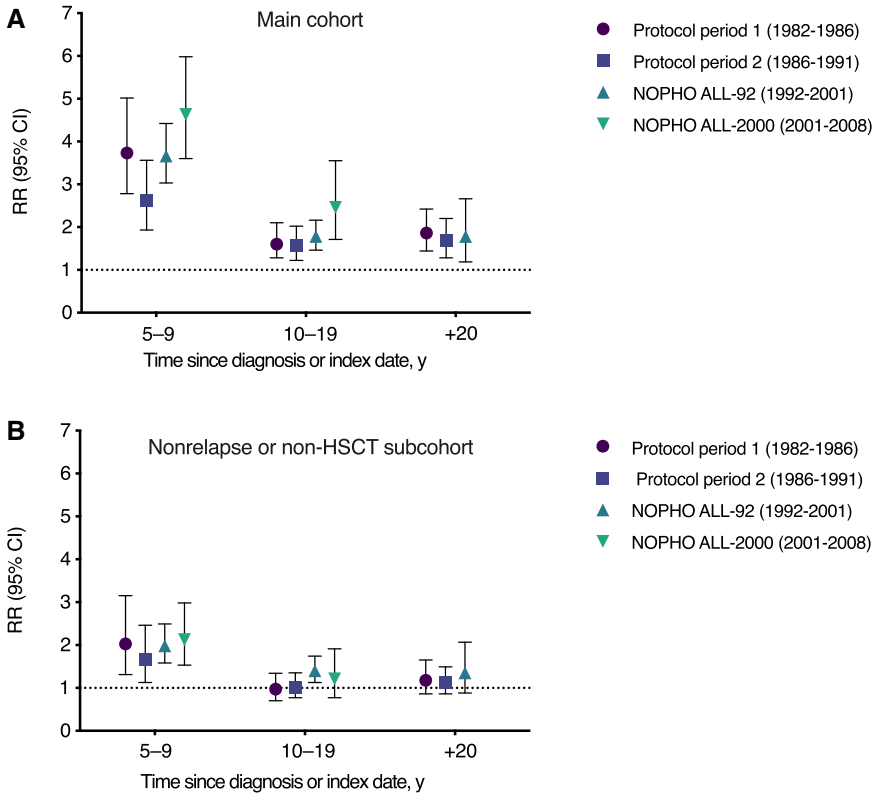


Figure 2. Overall disease-specific hospitalization rate ratio (RR) in 5-year survivors of childhood acute lymphoblastic leukemia (ALL) relative to matched population comparisons without of childhood cancer by time since diagnosis or index date and treatment protocol period. Results are shown for (**A**) main cohort and (**B**) nonrelapse or non-HSCT subcohort. Analyses were adjusted for sex, year of birth, and country. CI = confidence interval; HSCT = hematopoietic stem cell transplantation; NOPHO = Nordic Society of Paediatric Haematology and Oncology.

To investigate the total burden of hospitalizations per individual over time, we calculated the mean cumulative count for all disease-specific hospital admissions, also including readmissions, taking the competing risk of death into account (31). The mean cumulative count plots were stratified by ALL risk group and treatment protocol period. All statistical analysis was done in R version 3.6.3 packages "mets," "survival," and "ggplot2" (32).

Ethics

The study was conducted according to ethical and legal requirements of each country. The SALiCCS research program has been approved by Statistics Denmark and the Regional Ethical Review Board in Stockholm, Sweden (dnr 2016/25–31/5, 2016/1561–32, 2017/1656–32, 2017/1990–32, 2017/2340–32, 2018/1165–32).

Results

A total of 2024 5-year survivors of childhood ALL were followed for a median of 20 years from ALL diagnosis (interquartile range = 14-26). Characteristics of the study population are shown in Table 1. In the main cohort of ALL survivors, the overall rate of first-time disease-specific hospitalizations was more than twice as high as in the matched population comparisons (RR = 2.30, 95% CI = 2.09 to 2.52). When excluding survivors with relapse and/or HSCT, the RR decreased to 1.41 (95% CI = 1.27 to 1.58) (Table 2). The overall rate, relative to comparisons, was highest among HR patients and during the first 5 years of follow-up (ie, 5-10 years from diagnosis or index date) (Table 2). The RR for new disease-specific, first-time hospitalizations remained increased more than 20 years after diagnosis in the main cohort (RR = 1.78, 95% CI = 1.48 to 2.13). We found that also the non-irradiated survivors diagnosed 1986-2008, who did not had a relapse or received HSCT, had an increased overall hospitalization rate ratio relative to comparisons (RR = 1.41, 95% CI = 1.22 to 1.62) (Table 2). Relative to comparisons, we found no pattern of decrease in overall hospitalization rate ratio over the different treatment protocol periods by time since diagnosis periods (Figure 2; Supplementary Table 3, available online). In the main cohort, childhood ALL was associated with increased rates of hospitalization in all main disease groups (Figure 3). The highest RRs in both cohorts were seen for malignant neoplasms and for diseases of the blood.

At 30 years from diagnosis or index date, the cumulative incidence of a first hospitalization for any disease was 50% (95% CI = 47% to 54%) for ALL survivors and 34% (95% CI = 33% to 36%) for comparisons. In the nonrelapsed or non-HSCT subcohort, the 30-year cumulative incidences were 44% (95% CI = 40% to 48%) for survivors and 34% (95% CI = 33% to 36%) for comparisons (Supplementary Figure 1, available online).

At 30 years post ALL diagnosis, the mean cumulative number of multiple and recurrent disease-specific hospitalizations in the main cohort was on average 1.69 (95% CI = 1.47 to 1.90) per survivor and 0.80 (95% CI = 0.73 to 0.86) per matched comparison. In the subcohort without HSCT and relapse, the equivalent numbers were 1.08 (95% CI = 0.91 to 1.25) and 0.82 (95% CI = 0.74 to 0.89), respectively (Figure 4). The mean cumulative number of multiple and recurrent hospitalizations was highest among survivors of HR and IR treatment. At 30 years post diagnosis, an

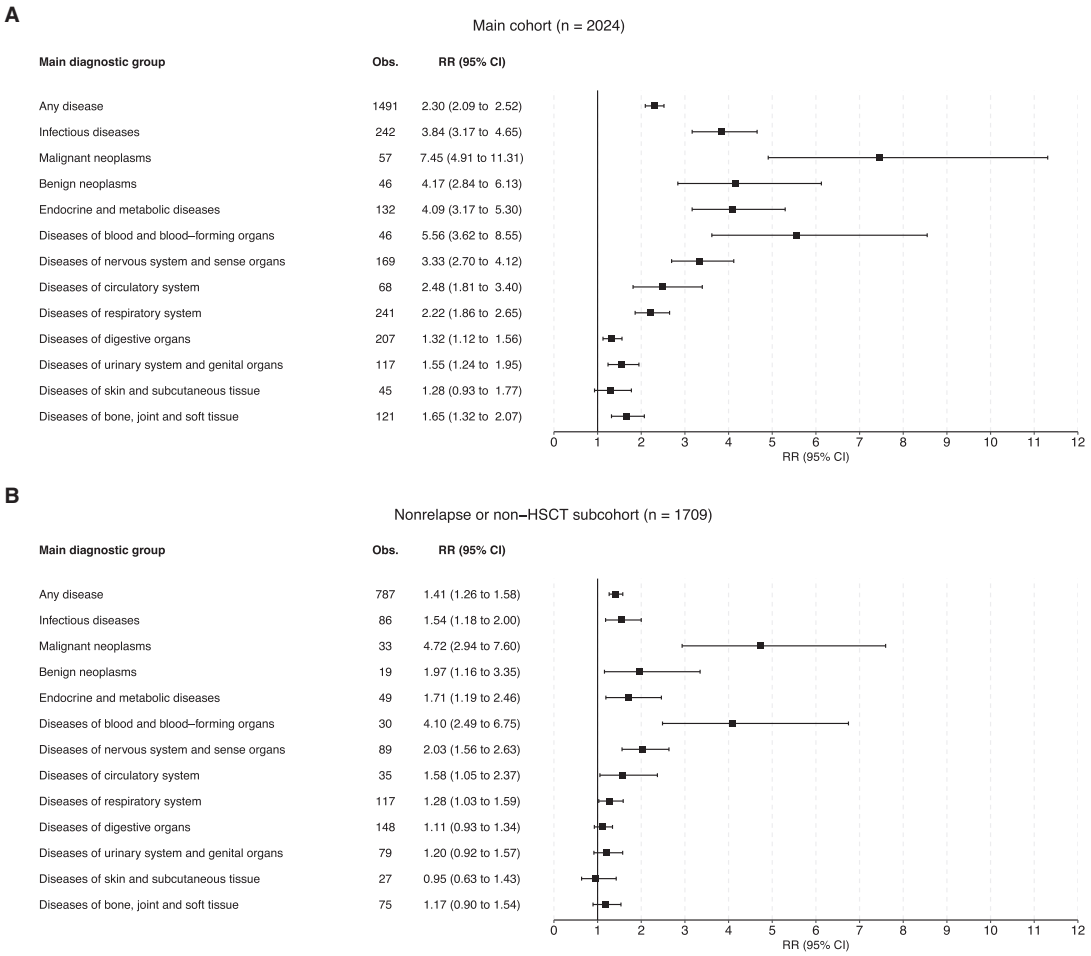


Figure 3. Risk of hospitalization in each of the 12 main diagnostic groups in 5-year survivors of childhood acute lymphoblastic leukemia (ALL) relative to matched population comparisons without of childhood cancer. Results are shown for (**A**) main cohort, and (**B**) nonrelapse or non-HSCT subcohort. Each person can be hospitalized for more than 1 of the specific disease categories within each main diagnostic group (please see "Methods" section for details). Analyses were adjusted for sex, year of birth, country, and calendar time period of diagnosis or index date (1982-1991, 1992-2001, and 2002-2008). CI = confidence interval; HSCT = hematopoietic stem cell transplantation; Obs. = observed number of first-time hospitalizations for a selected set of medical conditions (120 disease categories) among ALL survivors; RR = disease-specific hospitalization rate ratio.

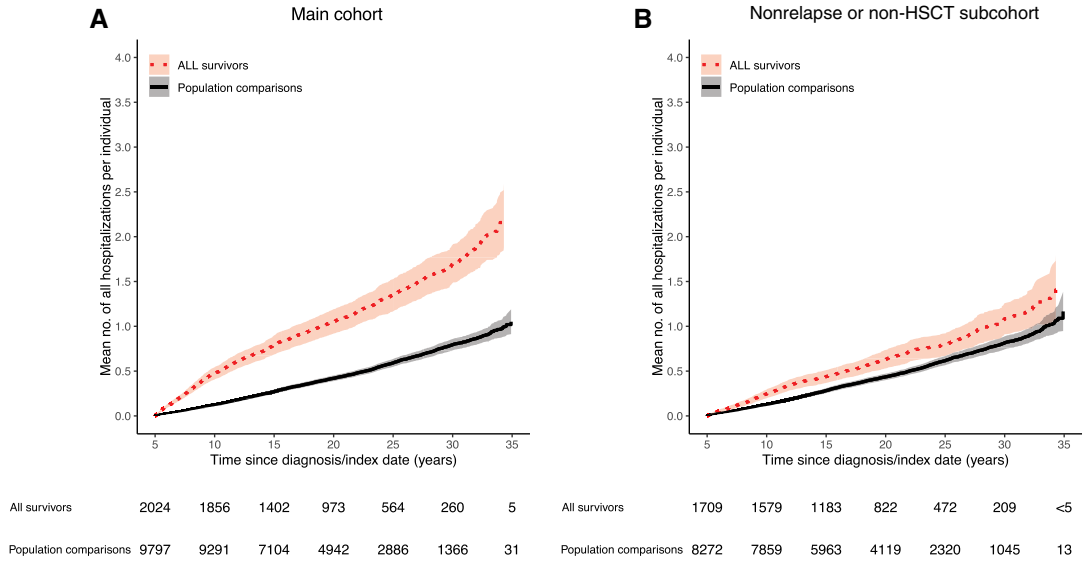
ALL survivor classified to receive HR treatment had on average 2.13 (95% CI = 1.65 to 2.61) hospitalizations; in comparison, an ALL survivor classified to receive SR treatment had 1.25 (95% CI = 0.99 to 1.51) hospitalizations on average (Figure 5). When investigating the effect of different treatment protocols on the mean cumulative number of multiple and recurrent hospitalizations, we found no remarkable differences between the 4 protocol periods in either the main cohort or subcohort (Supplementary Figure 2, available online).

In the restricted cohort with complete in- and outpatient hospitalization follow-up, adding outpatient hospital contacts did not markedly change the overall rate of first-time disease-specific hospitalizations for the subcohort and slightly decreased the rate for the main cohort (Supplementary Table 4, available online).

Discussion

In this population-based 2-country-wide cohort study with a follow-up period up to 35 years, 5-year ALL survivors had a more than twofold increased rate of hospitalization for somatic diseases compared with matched population comparisons. However, for the large subcohort that was successfully cured without experiencing a relapse or requiring HSCT, the hospitalization rate was only modestly higher than in individuals without a childhood cancer. The absolute mean numbers of multiple and recurrent hospitalizations were generally low.

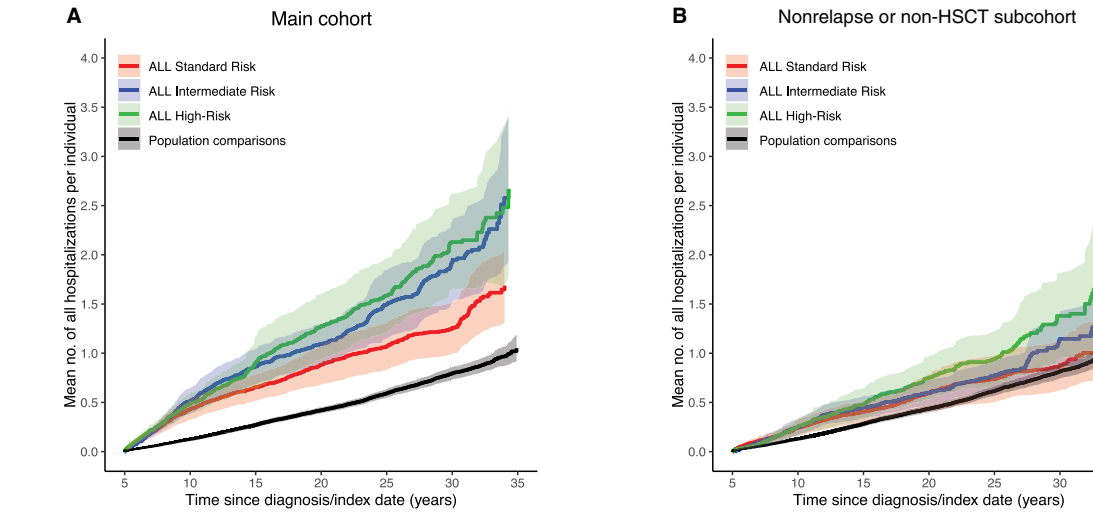
The study is based on high-quality register-based data from the Nordic countries. It is the first study, to our knowledge, to describe the overall risk of disease-specific hospitalizations in a large population-based cohort of ALL survivors, with the ability to separately assess the risk among survivors that did not receive HSCT or treatment for relapse. We describe the overall rate of disease-specific hospitalization and within each main diagnostic (organ specific) ICD group of disease, as was previously done among the combined group of all ALL survivors (11). In addition, we provide novel estimates of the magnitude of the disease-specific hospitalization burden by including both multiple and recurrent hospitalizations. The register-based design within the tax-supported health-care system in Denmark and Sweden ensures virtually complete long-term follow-up for medically verified conditions among both survivors and a large cohort of population comparisons.



All survivors	2024	1856	1402	973	564	260	5
Population comparisons	9797	9291	7104	4942	2886	1366	31

All survivors	1709	1579	1183	822	472	209	<5
Population comparisons	8272	7859	5963	4119	2320	1045	13

Figure 4. Mean cumulative count of multiple and recurrent disease-specific hospitalizations for 5-year survivors of childhood acute lymphoblastic leukemia (ALL) and matched population comparisons without childhood cancer. Results are shown for (**A**) main cohort and (**B**) nonrelapse or non-HSCT subcohort. **Shaded areas in transparent colors** around the lines of the estimates represent 95% confidence intervals. HSCT = hematopoietic stem cell transplantation.



ALL Standard Risk	766	720	550	382	239	124	<5
ALL Intermediate Risk	739	670	520	348	186	74	<5
ALL High-Risk	519	466	332	243	139	62	–
Population comparisons	9797	9291	7104	4942	2886	1366	31

ALL Standard Risk	679	629	475	328	199	98	<5
ALL Intermediate Risk	631	581	445	296	154	59	<5
ALL High-Risk	399	369	263	198	119	52	–
Population comparisons	8272	7859	5963	4119	2320	1045	13

Figure 5. Mean cumulative count of multiple and recurrent disease-specific hospitalizations for 5-year survivors of childhood acute lymphoblastic leukemia (ALL) stratified by treatment risk stratification group and for matched population comparisons without childhood cancer. Results are shown for (**A**) main cohort and (**B**) nonrelapse or non-HSCT subcohort. **Shaded areas in transparent colors** around the lines of the estimates represent 95% confidence intervals. HSCT = hematopoietic stem cell transplantation.

Registry-based studies have inherent limitations. In our main analysis, we captured primary discharge diagnostic codes for diseases severe enough to require inpatient hospitalization. Consequently, we did not capture information on conditions treated in the primary care or in the outpatient settings (eg, type 2 diabetes, hypertension, and infertility). We therefore potentially underestimated the total burden of late effects in our population. However, in the restricted, more recent study period in which outpatient data were available, inclusion of hospital-based outpatient visits did not markedly change the overall estimates. It is possible that our results were affected by increased medical surveillance of the ALL survivors, especially during the first 5 years of follow-up. However, because we relied on primary discharge diagnosis for disease-specific inpatient hospitalizations and furthermore did not include hospitalization in the ICD section "symptoms and ill-defined conditions," we assess the risk of surveillance bias as limited.

In our previous study, based on all childhood leukemia survivors diagnosed in 1970-2008 in 4 Nordic countries, the overall disease-specific standardized hospitalization rate for ALL

survivors relative to comparisons was 1.95 (95% CI = 1.83 to 2.07) (11). This is comparable with the overall result in this study, although the methods, study population, and follow-up periods differ. In our previous study, we had no treatment information. Few studies are directly comparable with ours, because the long-term risk of hospitalizations for multiple disease categories across several organ systems has primarily been conducted among all childhood cancer survivors combined, and, if reported separately, results for ALL survivors are often combined with other leukemia survivors (13,33-40) and in some studies also combined with lymphoma survivors (41,42). Only 2 studies have focused exclusively on overall hospitalization risk among ALL survivors, but the sample sizes were only approximately 200 (14,15).

The previously described higher risk of self-reported severe chronic health condition within the relapse or HSCT group of survivors (6,7) is in line with the excess risk of medically verified disease-specific hospitalizations documented in this study. When excluding survivors with relapse and HSCT, the rate of hospitalization decreased within all main diagnostic groups. The highest rate ratios were seen for SMN and diseases of the blood. The large drop in the rate ratio for infectious diseases in the subcohort is probably related to removal of hospitalization for acute infections related to ongoing treatment for relapse. Although the optimal model of personalized cancer follow-up care is yet to be elucidated (43), our results indicate that future efforts to reduce the risk of late hospitalizations among ALL survivors should mainly focus on survivors treated for HR ALL, survivors who received HSCT, and relapsed patients.

Over time there has been a gradual omission of cranial irradiation and a concurrent increase in the use of asparaginase, dexamethasone, and high-dose methotrexate (7,23,24). The North American childhood cancer survivor study cohort showed stable cumulative incidence for severe chronic health conditions over different time periods of diagnosis (44). Similarly, we found stable overall risk of hospitalization despite the improved survival over time for the HR and relapse patients (7).

In conclusion, survivors of childhood ALL had an elevated risk of hospitalization for somatic diseases relative to population comparisons, but the absolute mean numbers of multiple and recurrent hospitalizations were generally low. For the large subgroup of ALL survivors who were successfully cured without a relapse or HSCT, the hospitalization rate was only modestly higher than in individuals without a childhood cancer. Our findings are informative for both survivors and clinicians and are reassuring for most survivors treated for childhood ALL.

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Data Availability

The data underlying this article cannot be shared publicly because of ethical/privacy reasons.

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