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Long-Term Risk of Hospitalization Among Five-Year Survivors of Childhood Leukemia in the Nordic Countries

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Abstract

Background: Adverse effects from childhood leukemia treatment may persist or present years after cure from cancer. We provide a comprehensive evaluation of subsequent hospitalization in five-year survivors of childhood acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML).

Methods: In the Adult Life after Childhood Cancer in Scandinavia Study, we identified 4003 five-year survivors diagnosed with childhood leukemia 1970–2008 in Denmark, Sweden, Iceland, and Finland. Survivors and 129 828 population comparisons were followed for first-time nonpsychiatric hospitalizations for 120 disease categories in the hospital registries. Standardized hospitalization rate ratios and absolute excess rates were calculated. All statistical tests were two-sided.

Results: Survivors of ALL ($n = 3391$), AML ($n = 389$), and CML ($n = 92$) had an increased overall hospitalization rate compared with population comparisons. The rate ratio for any hospitalization was 1.95 (95% confidence interval [CI] = 1.83 to 2.07) in ALL, 3.09 (95% CI = 2.53 to 3.65) in AML, and 4.51 (95% CI = 3.03 to 6.00) in CML survivors and remained increased even 20 years from leukemia diagnosis. Corresponding absolute excess rates per 1000 person-years were 28.48 (95% CI = 24.96 to 32.00), 62.75 (95% CI = 46.00 to 79.50), and 105.31 (95% CI = 60.90 to 149.72).

Conclusion: Leukemia survivors have an increased rate of hospitalization for medical conditions. We provide novel insight into the relative and absolute rate of hospitalization for 120 disease categories in survivors of ALL, AML, and CML, which are likely to be informative for both survivors and healthcare providers.

Leukemia is the most common cancer in childhood (1), and with great advances in diagnostics and therapeutic approaches during the past half-century, survival rates have increased dramatically (2–5). The improved survival in acute leukemia is a result of a better risk stratification, use of intensive combination chemotherapy, and improved supportive care (3,4). For chronic myeloid leukemia (CML) patients, the introduction of tyrosine kinase inhibitors in the early 2000s has played an important role (5). However, the treatments that have improved survival are not without consequences. Adverse effects from childhood leukemia treatment may persist or present years after cure from cancer (6–9), and with the steeply growing population of

childhood leukemia survivors, a comprehensive characterization of long-term health consequences of past and current therapies has become increasingly important (10,11). The majority of previous studies reported exclusively either on survivors of acute lymphoblastic leukemia (ALL) (6,7,12–16) or on childhood cancer or childhood leukemia survivors overall and did not differentiate between subtypes of leukemia (8,17–24). Few studies reported on acute myeloid leukemia (AML) survivors (9, 25,26), and especially for childhood CML survivors there is a knowledge gap regarding the long-term risk of late effects (27). Several studies have reported on the long-term morbidity in childhood cancer survivors using hospitalizations for main diagnostic

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groups of diseases as outcome (12,20–24,28); however, most were not able to explore the underlying disease-specific categories of hospitalization. In the present study, we provide a detailed and comprehensive evaluation of the long-term risk of nonpsychiatric hospitalization for 120 disease-specific categories in five-year survivors of ALL, AML, and CML.

Methods

Cancer Survivor and Population Comparison Cohorts

This study is part of the large-scale population-based Nordic study Adult Life after Childhood Cancer in Scandinavia (ALiCCS) (29). From the basic childhood cancer cohort of 30 248 patients from Denmark, Finland, Iceland, and Sweden diagnosed with any type of childhood cancer before age 20 years between January 1, 1970 and December 31, 2008, we identified all patients who according to the International Classification of Childhood Cancer were diagnosed with leukemia ($n = 7609$) (Figure 1) (30, 31). The Nordic cancer registries are all population-based, with close to complete registration (32). We obtained information on type of cancer and date of diagnosis from the cancer registries.

The Nordic countries provide tax-supported public health care, including free access to hospitals. Utilization of health-care services is recorded in nationwide registers using a unique personal identification number as key. The identification number, assigned to all residents at birth or immigration, allows accurate linkage across registers (33).

To measure reference rates of morbidity, we selected a population comparison cohort from the national population registries. For each patient from the basic childhood cancer cohort including all types of childhood cancers, five comparisons were randomly selected from all those who were alive on the date of the cancer diagnosis of the corresponding patient (index date), of the same sex, age, and country (Denmark, Finland, and Iceland) or county (Sweden) of residence, and without a cancer diagnosis before the age of 20 years (Figure 1). For both patients and population comparisons, we obtained information on vital status and emigration during follow-up in the population registers.

Before linkage of leukemia patients and population comparisons to the respective national hospital registries, we excluded those in whom more than one cancer was diagnosed during childhood ($n = 52$), those with less than 5 years of follow-up, as well as those with more than 5 years from leukemia diagnosis/index date to start date of the national hospital registries to ensure complete hospital history (Sweden, stepwise inclusion of counties in 1964–1987 and nationwide since 1987; Finland, 1969; Denmark, 1977; Iceland, 1999). These exclusions resulted in a cohort of 4130 five-year survivors of childhood leukemia and a reference cohort of 130 056 individuals (Figure 1). Survivors were grouped into ALL, AML, CML, and “other and unspecified leukemia” according to the International Classification of Childhood Cancer (Supplementary Table 1, available online).

Hospital Admissions

The national hospital registers hold information on virtually all nonpsychiatric hospital admissions. Each admission to hospital initiates a record, which includes the personal identification number, dates of admission and discharge, a primary discharge diagnosis, and a varying number of supplementary diagnoses coded according to the International Classification of Diseases (ICD), 8th to 10th revisions (ICD-8 to ICD-10) (34–37).

Data on leukemia survivors and comparisons were linked to the hospital registries, and a full hospital admission history was established for each person. We excluded 127 leukemia survivors and 228 comparisons who had been admitted to hospital for a chromosomal abnormality (ICD-8 codes 759.3–759.5, ICD-9 code 758, and ICD-10 codes Q90–99), because these conditions may confound associations between leukemia and several of the outcomes. Thus, 4003 five-year survivors of childhood leukemia and 129 828 population comparisons remained for risk analyses (Figure 1).

We grouped the hospital diagnoses into 120 disease-specific categories, which in turn were assembled into 12 main diagnostic groups. Diagnostic categories of ICD-9 and ICD-10 were adapted to ICD-8 (Supplementary Table 2, available online). We did not include the ICD sections on symptoms and ill-defined conditions, injuries, violence, and accident as well as complications during pregnancy, delivery, and puerperium. For information on second malignant neoplasm among leukemia survivors and first primary cancers among comparisons, we used the cancer registries.

Statistical Analysis

Follow-up for diseases other than cancer was started 5 years after the date of leukemia diagnosis for survivors and 5 years after index date for population comparisons. Follow-up for a second malignant neoplasm in survivors and a first primary cancer in population comparisons started at the age of 20 years at the earliest. Follow-up ended on date of death, date of emigration, or end of study (Iceland: December 31, 2008; Sweden: December 31, 2009; Denmark: October 31, 2010; Finland: December 31, 2012), whichever occurred first. Only the primary diagnosis (the main reason for hospitalization) for each hospital admission was included in the analyses. If an individual was admitted to the hospital more than once for a particular disease, only the first record was retained. The number of first hospitalizations was added up in 12 main diagnostic groups, and the overall number of hospitalizations was defined as first-time hospitalization for one or more of the 120 diseases. For ALL, AML, and CML, survivors' rates were analyzed for each disease category, for the main diagnostic groups, and for overall hospitalization.

The observed number of first hospitalizations of survivors of childhood cancer for a given disease category was compared with expected numbers derived from the appropriate sex-, age-, and calendar period-specific hospitalizations of the population comparison cohort, and standardized hospitalization rate ratios (RRs) were estimated. The absolute excess rate (AER) was calculated as the difference between the observed and expected hospitalization rates per 1000 person-years of follow-up. The 95% confidence intervals of the RR and AER were estimated with Fieller's theorem on the assumption that the observed number of first hospitalizations followed a Poisson distribution (38). Tests for heterogeneity and trend were calculated using two-sided Wald tests in Poisson models adjusted for sex, age, calendar period, and country. A P value of less than .05 was considered statistically significant.

The overall rate of hospitalization was stratified by sex, type of leukemia, age at leukemia diagnosis (five-year interval), and time since leukemia diagnosis (0–9, 10–19, ≥ 20 years). For the largest group of survivors (ALL) we were able to further stratify by both time since leukemia diagnosis and decade of leukemia diagnosis (1970–1979, 1980–1989, and 1990–1999). ALL survivors diagnosed 2000–2008 were not included in this analysis due to limited follow-up in hospital registries.

Figure 1. Flow diagram showing exclusions from the study cohorts. Index date is defined as the date of the cancer diagnosis of the corresponding patient. Study follow-up ended on date of death, date of emigration, or end of study (Iceland: December 31, 2008; Sweden: December 31, 2009; Denmark: October 31, 2010; Finland: December 31, 2012), whichever occurred first. Start date of the respective national hospital registries: Sweden, stepwise inclusion of counties in 1968–1987 and nationwide since 1987; Finland, 1969; Denmark, 1977; Iceland, 1999.

To illustrate risk on an absolute scale for each type of leukemia and population comparisons, cumulative incidence by time since leukemia diagnosis/index date was calculated including first-time hospitalization for any disease only, where death was treated as a competing risk (39). To compare the three types of leukemia directly, the rate of first-time hospitalization for any disease was investigated using a Cox proportional hazard model with time since leukemia diagnosis as the underlying time scale, and censoring for the competing event, death. The model was adjusted for sex, age at leukemia diagnosis, and decade of leukemia diagnosis, and the assumption of proportionality was verified graphically. Finally, we conducted a post-hoc analysis

estimating the RR of being hospitalized for injuries, because this is an outcome of external origin and therefore not expected to be increased among leukemia survivors. The statistical software STATA version 14 and SAS version 9.3 were used. The study was approved by the national bioethics committees, the data protection authorities, or the national institute for health and welfare in the respective countries.

Results

The inpatient disease burden was characterized and quantified among 4003 five-year childhood leukemia survivors. Patients

Table 1. Survivor characteristics of the study population of 4003 five-year childhood leukemia survivors

Survivor characteristics	Type of leukemia*, No. (%)				
	All types of leukemia combined	ALL	AML	CML	Other
Overall	4003 (100.0)	3391 (100.0)	389 (100.0)	92 (100.0)	131 (100.0)
Sex					
Male	2125 (53.1)	1834 (54.1)	182 (46.8)	51 (55.4)	58 (44.3)
Female	1878 (46.9)	1557 (45.9)	207 (53.2)	41 (44.6)	73 (55.7)
Age at leukemia diagnosis, y					
0–4	2023 (50.5)	1811 (53.4)	136 (35.0)	7 (7.6)	69 (52.7)
5–9	979 (24.5)	865 (25.5)	72 (18.5)	14 (15.2)	28 (21.4)
10–14	601 (15.0)	480 (14.2)	84 (21.6)	22 (23.9)	15 (11.5)
15–19	400 (10.0)	235 (6.9)	97 (24.9)	49 (53.3)	19 (14.5)
Time-period of leukemia diagnosis					
1970–1979	468 (11.7)	387 (11.4)	26 (6.7)	15 (16.3)	40 (30.5)
1980–1989	1074 (26.8)	959 (28.3)	85 (21.9)	10 (10.9)	20 (15.3)
1990–1999	1456 (36.4)	1241 (36.6)	154 (39.6)	35 (38.0)	26 (19.9)
2000–2008	1005 (25.1)	804 (23.7)	124 (31.9)	32 (34.8)	45 (34.4)
Country of origin					
Sweden	1721 (43.0)	1461 (43.1)	157 (40.4)	37 (40.2)	66 (50.4)
Finland	1250 (31.2)	1059 (31.2)	114 (29.3)	35 (38.0)	42 (32.1)
Denmark	1014 (25.3)	855 (25.2)	117 (30.1)	20 (21.7)	22 (16.8)
Iceland	18 (0.5)	16 (0.5)	1 (0.3)	0 (0.0)	1 (0.8)
Time since diagnosis, y					
5–9	1042 (26.0)	824 (24.3)	123 (31.6)	43 (46.7)	52 (39.7)
10–19	1474 (36.8)	1244 (36.7)	160 (41.1)	38 (41.3)	32 (24.4)
≥20	1487 (37.2)	1323 (39.0)	106 (27.3)	11 (12.0)	47 (35.9)
Median years of follow-up from diagnosis (range)	16 (5–42)	17 (5–42)	14 (5–41)	11 (5–36)	12 (5–41)

*ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CML = chronic myeloid leukemia; Other = other and unspecified leukemia.

with ALL (n = 3391) accounted for 84.7% of all leukemia survivors, AML (n = 389) for 9.7%, CML (n = 92) for 2.3%, and patients with other and unspecified leukemia (n = 131) for 3.3%. Characteristics of the leukemia survivors are shown in [Table 1](#). Survivors were followed in the national hospital registers for 49 649 person-years with a median follow-up of 16 years from leukemia diagnosis (range 5–42 years).

Overall, 1490 (37.2%) leukemia survivors were ever hospitalized for any disease during follow-up. These survivors experienced 2898 first admissions to hospital for one or more of the 120 specified disease categories, yielding an RR of 2.08 (95% confidence interval [CI] = 1.96 to 2.20) ([Table 2](#)). The overall AER was 32.44 per 1000 person-years (95% CI = 28.94 to 35.94), meaning that three excess hospitalizations were observed for each additional year of follow-up of 100 survivors. Compared with the general population, survivors of CML had the highest relative and absolute rate (RR = 4.51, 95% CI = 3.03 to 6.00; AER = 105.31 per 1000 person-years, 95% CI = 60.90 to 149.72) followed by AML (RR = 3.09, 95% CI = 2.53 to 3.65; AER = 62.75 per 1000 person-years, 95% CI = 46.00 to 79.50) and ALL (RR = 1.95, 95% CI = 1.83 to 2.07; AER = 28.48 per 1000 person-years, 95% CI = 24.96 to 32.00). The overall RR remained increased even at 20 or more years after leukemia diagnosis compared with the general population ([Table 2](#); [Supplementary Figure 1](#), available online).

The RR and 95% CI by decade of leukemia diagnosis for ALL survivors who were 5–9 years from leukemia diagnosis were: 1970s, 2.22 (1.76 to 2.79); 1980s, 2.53 (2.21 to 2.89); and 1990s, 2.89 (2.53 to 3.30) ($P_{\text{trend}} < .001$); for ALL survivors who were 10–19 years from diagnosis: 1970s, 1.27 (1.03 to 1.56); 1980s, 1.60 (1.41 to 1.81); 1990s, 1.52 (1.30 to 1.77) ($P_{\text{trend}} < .001$); and for ALL survivors who were ≥20 years from diagnosis: 1970s, 1.71 (1.41

to 2.08); 1980s, 1.80 (1.53 to 2.12); 1990, 1.30 (0.67 to 2.54) ($P_{\text{trend}} < .001$) ([Figure 2](#)).

[Figure 3](#) shows the observed numbers of hospitalizations and RR estimates for the 12 main diagnostic groups by type of leukemia. The RR was increased for all main diagnostic groups. Highest RRs were seen for second malignant neoplasms among ALL survivors and diseases of blood for AML and CML survivors. Among ALL survivors, the highest AER was seen for infectious diseases, and among AML and CML survivors the highest AERs were found for diseases of the respiratory system ([Supplementary Tables 3 and 4](#), available online).

A comprehensive list of RR and AER for all of the 120 specific disease categories for each type of leukemia is provided in [Supplementary Tables 3 and 4](#) (available online). For all types of leukemia, the AERs for the specific disease categories were generally low. Among survivors of ALL we found particularly high relative rates of testicular dysfunction, herpes zoster, pituitary hypofunction, and secondary CNS tumors compared with population comparisons ([Table 3](#)). In survivors of AML, high relative rates were seen for cataract and heart failure. Among CML survivors the most prevalent first-time hospitalizations were diseases of bone and joints (n = 10), pneumonia (n = 9), and cataract (n = 6).

[Figure 4](#) shows that 50.1% (95% CI = 47.7 to 52.5) of ALL survivors and 36.2% (95% CI = 35.2 to 37.3) of the comparisons had at least one first hospitalization for any disease 25 years after diagnosis/index date. Among AML survivors the proportions were 52.7% (95% CI = 47.0 to 58.5) and 36.9% (95% CI = 34.1 to 39.8), respectively. For CML a total of 61.0% (95% CI = 50.8 to 71.1) of the survivors and 37.2% (95% CI = 31.1 to 43.2) of the comparisons had a first-time hospitalization 25 years after diagnosis/index date.

Table 2. RRs and AERs in 4003 five-year childhood leukemia survivors by survivor characteristics*

Survivor characteristics	Person-years at risk	Observed No. of disease-specific hospitalizations†	RR (95% CI)	AER (95% CI) per 1000 person-years
Overall	49 649	2898	2.08 (1.96 to 2.20)	32.44 (28.94 to 35.94)
Sex				
Male	25 273	1402	2.12 (1.95 to 2.29)	31.63 (26.96 to 36.30)
Female	24 376	1496	2.04 (1.88 to 2.21)	33.43 (28.18 to 38.67)
$P_{\text{heterogeneity}}$			.51	.62
Type of leukemia				
ALL	43 283	2365	1.95 (1.83 to 2.07)	28.48 (24.96 to 32.00)
AML	4068	352	3.09 (2.53 to 3.65)	62.75 (46.00 to 79.50)
CML	697	97	4.51 (3.03 to 6.00)	105.31 (60.90 to 149.72)
Other	1601	84	1.68 (1.14 to 2.21)	20.24 (4.22 to 36.26)
$P_{\text{heterogeneity}}$			<.001	<.001
Age at leukemia diagnosis, y				
0–4	25 421	1301	1.95 (1.80 to 2.10)	28.37 (23.86 to 32.87)
5–9	13 080	752	1.98 (1.76 to 2.21)	29.47 (22.74 to 36.21)
10–14	7008	503	2.32 (1.99 to 2.64)	39.49 (29.75 to 49.23)
15–19	4141	342	2.61 (2.15 to 3.08)	48.35 (34.33 to 62.38)
P_{trend}			.001	<.001
Time since diagnosis, y				
5–9	17 136	1292	3.01 (2.78 to 3.24)	62.68 (55.56 to 69.80)
10–19	21 680	1020	1.62 (1.50 to 1.76)	18.52 (14.48 to 22.57)
≥20	10 832	586	1.78 (1.58 to 1.98)	22.55 (16.76 to 28.33)
P_{trend}			<.001	<.001

*All statistical tests are two-sided. RR = standardized hospitalization rate ratio. AER = absolute excess rate; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CI = confidence interval; CML = chronic myeloid leukemia; Other = other and unspecified leukemia;

†First-time hospitalizations for a selected set of medical conditions (120 disease categories); each person may be hospitalized for more than one specific disease category. See Methods for details.

Figure 2. Standardized hospitalization rate ratio for five-year survivors of acute lymphoblastic leukemia, by time period since leukemia diagnosis, and stratified by decade of leukemia diagnosis. Error bars indicate 95% confidence intervals (CI). Decades of leukemia diagnosis = 1970–1979, 1980–1989, and 1990–1999.

Using ALL survivors as reference, we were able to directly compare the adjusted overall hazard rate of a first-time hospitalization among the specific types of leukemia. We found that both AML (hazard ratio = 1.25, 95% CI = 1.05 to 1.49) and CML (hazard ratio = 2.22, 95% CI = 1.63 to 3.04) survivors had higher rates of hospitalization for any disease compared with ALL survivors.

In a post-hoc analysis, we investigated the RR of hospitalization for injuries and found no increased rate of hospitalization among leukemia survivors compared to population comparisons (RR = 1.01, 95% CI = 0.91 to 1.12) ([Supplementary Table 5](#), available online).

Discussion

In this population-based study of 4003 five-year childhood leukemia survivors, we found an overall twofold increased rate of hospitalization for medical conditions compared with the general population. For the first time, to our knowledge, we provide insight into the relative and absolute rate of hospitalization for 120 disease categories in survivors of ALL, AML, and CML, respectively. The pattern of hospitalizations differed between the subtypes of leukemia with higher hospitalization rates among CML and AML survivors compared with ALL survivors. The observed differences likely reflect that a higher proportion of AML and CML survivors received stem cell transplantation (SCT), which is a known risk factor for late effects in virtually every organ system (40, 41). Because our cohort was treated before the tyrosine kinase inhibitor era, virtually all CML survivors received SCT.

Despite methodological differences between our study and previous studies on morbidity among leukemia survivors, overall results are quite similar (6, 9, 11, 24, 42–45). The cumulative incidence at 25 years from diagnosis of any reported chronic medical condition among five-year ALL survivors was 65% (95% CI = 61 to 69) in the North American Childhood Cancer Survivor Study cohort diagnosed 1970–1986, and that of any hospitalization was 50.1% (95% CI = 47.7 to 52.5) in this study (6). The lower risk in our study most likely reflects that we included only diseases serious enough to require hospital admission.

Our results of an increased rate of second malignant neoplasms are consistent with a study from the North American Childhood Cancer Survivor Study demonstrating a 4.4 and 6.4 times increased risk in ALL and AML survivors, respectively (46). We show a particularly high rate of CNS tumors after the age of 20 years among ALL survivors. Because we present data only on

Figure 3. Risk of hospitalization in each of 12 main diagnostic groups by type of leukemia. Results are shown for (A) acute lymphoblastic leukemia, (B) acute myeloid leukemia, and (C) chronic myeloid leukemia. Each person can be hospitalized for more than one of specific disease categories within each main diagnostic group (please see Methods for details). Obs. = observed number of hospitalizations; RR = standardized hospitalization rate ratio. CI = confidence interval.

late second malignant neoplasms occurring after the age of 20 years, we were not able to show an increased rate of secondary leukemia, most often occurring within the first 10 years after diagnosis (47).

A high proportion of the CML survivors were hospitalized for diseases of bone and joints (10 of 92), which is comparable to what has been found in survivors of adult CML (27, 48). We also found a high relative and AER of cataract, especially in AML and CML survivors. The increased rate of cataract has previously

been strongly associated with total body irradiation given as part of the conditioning regimen of SCT (27, 49).

CNS irradiation, a strong risk factor for a broad range of late effects, was replaced by intrathecal injections of methotrexate and high-dose systemic chemotherapy in almost all patients in the 1990s (50). In the Nordic countries, almost 60% of ALL patients diagnosed 1986–1991 received prophylactic CNS irradiation compared with less than 10% in patients diagnosed 1992–1996, and in the most recent Nordic treatment protocols CNS

Table 3. Observed and expected number of first-time hospitalizations with associated RR and AER for selected specific disease categories in five-year survivors of childhood ALL, AML, and CML*

Specific disease category	O/E No. of first hospitalizations	RR (95% CI)	AER (95% CI) per 1000 person-years
ALL (n = 3391)			
Testicular dysfunction	12/0.06	208.57 (56.88 to 764.75)	0.28 (0.12 to 0.43)
Herpes zoster	26/0.55	46.86 (27.35 to 80.26)	0.59 (0.36 to 0.82)
Pituitary hypofunction	33/0.73	45.07 (28.09 to 72.31)	0.75 (0.49 to 1.01)
CNS tumor	40/1.3	31.56 (21.77 to 45.76)	1.96 (1.33 to 2.58)
Cataract	53/1.8	29.60 (21.06 to 41.60)	1.20 (0.87 to 1.54)
Sepsis	69/3.6	19.31 (14.60 to 25.52)	1.52 (1.14 to 1.90)
Epilepsy	61/13	4.86 (3.73 to 6.32)	1.14 (0.78 to 1.50)
Pneumonia	119/31	3.86 (3.20 to 4.65)	2.08 (1.57 to 2.58)
AML (n = 389)			
Cataract	15/0.18	84.24 (48.91 to 145.08)	3.86 (1.88 to 5.83)
Heart failure	6/0.13	44.59 (19.38 to 102.61)	1.46 (0.27 to 2.66)
Sepsis	10/0.39	26.56 (13.74 to 48.95)	2.39 (0.85 to 3.92)
Pneumonia	15/2.7	5.56 (3.34 to 9.25)	3.08 (1.18 to 4.98)
Intestinal infectious diseases	14/3.2	4.41 (2.61 to 7.47)	2.76 (0.89 to 4.64)
Diseases of bone and joints	20/8.0	2.50 (1.61 to 3.88)	3.08 (0.83 to 5.32)
CML (n = 92)			
Cataract	6/0.04	135.92 (60.08 to 307.51)	9.37 (1.82 to 16.92)
Pneumonia	9/0.49	18.19 (9.44 to 35.02)	12.84 (3.96 to 21.71)
Diseases of bone and joints	10/1.6	6.16 (3.31 to 11.46)	13.09 (3.40 to 22.77)

*Selection criteria for ALL and AML survivors was defined as a RR lower 95% confidence limit of greater than 10 and/or an AER lower 95% confidence limit of greater than 0.7 and more than 5 observed first-time hospitalizations. Selection criterion for CML survivors was defined as more than 5 observed first-time hospitalizations. Please see [Supplementary Tables 3 and 4](#) (available online) for a comprehensive list of RR and AER for all 120 specific disease categories for each type of leukemia. RR = standardized hospitalization rate ratio; AER = absolute excess rate; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CI = confidence interval; CML = chronic myeloid leukemia; O/E = observed/expected.

irradiation has been eliminated (51, 52). Despite that, we found no decrease in the overall rate of hospitalizations across treatment decades compared to the general population. This might be due to a wider use of dexamethasone, methotrexate, and asparaginase, a more intensive maintenance therapy, and a successful salvage therapy in relapsed patients, including SCT, leading to more cumulated late effects among ALL survivors (53).

The main strengths of our study are the large cohort of childhood leukemia survivors, the use of high-quality registers with medically verified diagnoses, and the large randomly selected population comparison cohort. The population-based design with the use of unique personal identification numbers and the hospital registers ensures virtually complete, long-term follow-up for late effects severe enough to require inpatient hospitalization.

The study also has limitations. The cancer registries hold little information on treatment data; thus we were unable to associate specific treatment modalities with hospitalization patterns. Some hospitalizations in our study, particularly for infectious diseases, may be related to treatment for late relapse. However, most relapses occur within 5 years from leukemia diagnosis. In Nordic ALL patients the median time to relapse was 28 months after diagnosis (54). Less severe diseases treated in the outpatient setting or by general practitioners, for example type 2 diabetes, were not included because we used first-time hospital admissions as outcome. Accordingly, we acknowledge that we underestimate the absolute overall disease burden experienced by childhood leukemia survivors. This limitation also applies to the population comparisons; thus the validity of the RR estimates is left unaffected, although are restricted to medical conditions severe enough to require inpatient hospitalization. This may explain why we did not find an increased rate of,

for example, infertility as reported in other studies (55, 56). In addition, we cannot exclude the possibility that leukemia survivors might be under closer medical surveillance than population comparisons. However, because we included only diseases serious enough to require hospitalization in the tax-supported hospitals of the Nordic countries, the effect of surveillance bias is likely to be small.

In conclusion, five-year leukemia survivors had an overall increased rate of hospitalization that persisted well into adulthood compared with the general population. The pattern of hospitalization differed between subtypes of leukemia with higher hospitalization rates among CML and AML survivors compared with ALL survivors. With this study we provide novel insight into the relative and absolute rate of hospitalization for a broad range of medical conditions in survivors of ALL, AML, and CML, respectively. This comprehensive evidence is likely to be informative for both health-care providers and survivors and can be useful when preparing survivorship care plans for this large and important group of childhood cancer survivors.

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Notes

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Figure 4. Cumulative incidence for any hospitalization in leukemia survivors and matched population comparisons. Results are shown for (A) acute lymphoblastic leukemia (ALL), (B) acute myeloid leukemia (AML), and (C) chronic myeloid leukemia (CML).

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