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Seasonal variation in childhood acute lymphoblastic leukemia, but not in acute myeloid leukemia, or brain tumors – A Swedish population-based study

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ABSTRACT

Background: Acute lymphoblastic leukemia (ALL), the most common malignancy in children and adolescents, arises from a heterogeneous and multifactorial etiology involving genetic and environmental factors. Studies of seasonal variation in ALL diagnosis have yielded inconsistent results, likely reflecting differences in study design and population characteristics. Here, we evaluated seasonal variation across ALL immunophenotypes, including two common genetic subtypes.

Methods: We analyzed seasonal variation by ALL subtype in 1504 ALL patients diagnosed before the age of 18 between 1995 and 2017 using data from the National Cancer Register and the Swedish Childhood Cancer Registry. Subgroup analysis included 1305 B-cell precursor ALL (BCP-ALL) cases, including 422 high hyperdiploid (HeH) and 259 *ETV6::RUNX1* fusion-positive cases, and 175 T-cell ALL (T-ALL) cases. For comparison, 214 acute myeloid leukemia (AML) cases and 1367 brain tumor cases, including 224 medulloblastomas, were analyzed. Cases were grouped into overlapping 3-month diagnostic periods and analyzed using a Bayesian GARIMAX model, an extension of the autoregressive integrated moving average (ARIMA) framework. A sensitivity analysis was performed restricted to children aged 1–17 years.

Results: Seasonal variation was observed in the overall ALL cohort, with peaks between June and October. BCP-ALL and T-ALL also showed informative seasonality, with August consistently included among the peak months. Similar results were obtained in the sensitivity analysis. No seasonal variation was observed in AML, medulloblastoma, or other brain tumors. Informative seasonal variation was not detected in the HeH or *ETV6::RUNX1*-positive subgroups, although HeH showed peak quarters consistent with the overall ALL pattern.

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Conclusion: These findings support a role for seasonal triggers in ALL and warrant further investigation in larger, genetically stratified cohorts.

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer in children and adolescents under 18 years of age, accounting for approximately 25% of pediatric malignancies. The majority (~85%) of cases are of B-cell precursor (BCP-ALL) origin, a genetically heterogeneous disease characterized by recurrent genetic aberrations that define distinct subtypes, guide prognosis, and inform modern treatment strategies [1].

T-cell ALL (T-ALL) accounts for 10–15% of childhood ALL cases and advances in genome and transcriptome sequencing have delineated 15 distinct subtypes and identified potential avenues for future risk stratification [2,3]. Unlike BCP-ALL, genetic alterations in T-ALL are rarely reported to arise in utero [4]. The etiological factors are less well understood, partly due to limited epidemiological data, but reported contributors include genetic predisposition, ionizing radiation, and retroviral exposures [5–7].

To date, 24 genetically distinct subtypes of BCP-ALL have been described. The two most common subtypes — high hyperdiploid (HeH) (~30% of cases) and *ETV6*::*RUNX1* fusion-positive ALL (~25% of cases) are both associated with favorable outcomes [8,9]. These recurrent genetic aberrations are thought to initiate BCP-ALL by establishing a preleukemic clone, often in utero [10,11]. The *ETV6::RUNX1* fusion can be detected in the cord blood of 1–5% of healthy newborns, although only a small fraction (~0.2%) of these preleukemic clones progress to clinically overt leukemia [12]. Progression from a preleukemic state to clinical disease requires secondary somatic genetic aberrations [13,14] and the latency period from preleukemic state to overt leukemia can vary widely, even among twins carrying the same preleukemic clone [15].

Leukemia development has been reported to be influenced by a complex interplay of genetic susceptibility, prenatal and early-life environmental exposures, infections before and after birth, immune system maturation, and broader environmental factors such as pollution, radiation, and temperature [16–40]. Conversely, some exposures may be protective, including breastfeeding, daycare attendance, and early-life contact with pets, which are thought to stimulate immune development [36,37]. Evidence for other exposures, such as solar ultraviolet radiation, remains inconsistent [38–40]. The impact of these exposures may vary between molecular BCP-ALL subtypes [18,41–43], but subtype-specific risk profiles are poorly characterized, likely due to limited molecular data from large registry-based studies [44].

Seasonal variation refers to predictable fluctuations in disease incidence occurring at regular intervals, such as months or seasons. Seasonal patterns in infections have motivated studies of ALL diagnosis, with reported peaks particularly in BCP-ALL, but results are inconsistent, with peaks reported throughout the year (Supplementary Table 1). Poisson regression with harmonic terms, single-factor analyses, and standard ARIMA models are commonly used to study seasonality but have important limitations. Poisson models do not adequately account for overdispersion or temporal dependence, single-factor analyses are largely descriptive and ignore autocorrelation, and standard ARIMA models rely on distributional assumptions that are difficult to justify for sparse count data. To address these limitations, we used GARIMAX, a modified ARIMA-based method, to distinguish true seasonal variation from random fluctuations. We examined seasonal patterns across ALL immunophenotypes and the two most common BCP-ALL genetic subtypes in a nationwide Swedish cohort of patients diagnosed between 1995 and 2017.

2. Methods

2.1. Data sources

Sweden maintains comprehensive population registers that continuously capture demographic and healthcare data. All permanent residents receive a personal identity number, which enables linkage across registers. The Swedish Childhood Cancer Registry (SCCR), the Swedish National Cancer Register (NCR) [45], and the Total Population Register (TPR) [46] were the three data sources used in this study.

The SCCR is a national quality register covering children and adolescents with CNS tumors, solid tumors, and hematological malignancies. ALL and AML have been registered since the 1970s, and CNS and solid tumors since the 1980s. The overall coverage is about 90% [47], with underregistration mainly affecting benign tumors not requiring oncologic treatment; coverage for malignant tumors is therefore considered near-complete. For ALL, the register includes date of diagnosis, clinical characteristics, treatment, outcome, immunophenotype, genetic subtype, and other key genetic aberrations. The common BCP-ALL subtypes HeH and *ETV6::RUNX1*-positive ALL has been recorded since 1992 and 2000, respectively, following the introduction of reliable cytogenetic diagnostics.

The NCR is a nationwide, population-based registry that records all cancer diagnoses in Sweden. Established in 1958, it provides high-quality data with near-complete coverage of cancer incidence, making it a valuable resource for research and public health.

2.2. Participants

We identified a cohort of 1504 children and adolescents diagnosed with ALL from the SCCR and NCR, including 1305 BCP-ALL cases and 175 T-ALL cases; 24 cases were excluded due to missing immunophenotype data. Within the BCP-ALL cohort, the two major genetic subtypes were extracted: 422 HeH cases and 259 *ETV6::RUNX1* fusion-positive cases. In addition, 214 AML cases, 1367 brain tumors, including 224 medulloblastomas, were included for complementary analysis. All cases were diagnosed before 18 years of age, between January 1, 1995, and December 31, 2017.

To ensure data consistency, only cases recorded in both registers were included. Also, only individuals born and diagnosed in Sweden were included. A detailed flowchart outlining the data preparation process is provided in Fig. 1.

2.3. Statistical analysis

We modeled seasonal variation in quarterly diagnosis counts using a Bayesian generalized autoregressive integrated moving average with exogenous variables (GARIMAX) extension with a negative binomial likelihood, building on the standard autoregressive integrated moving average with exogenous variables (ARIMAX) framework [48]. ARIMAX is widely used for seasonality detection across fields [49–54]. The Negative Binomial distribution accounts for overdispersion common in sparse count data [55], while the Bayesian framework improves inference in small samples [56].

Seasonal effects were modeled by incorporating harmonic covariates as exogenous regressors in the GARIMAX model. Each model included a sine–cosine pair with a quarterly period, entered simultaneously to allow arbitrary phase (i.e., different peak timing). Using both sine and cosine in every model ensures that seasonal peaks need not align to a

fixed month. A seasonal effect was inferred with the posterior 95% credible interval for at least one of the harmonic coefficients excluded zero, implying a non-zero seasonal amplitude. Methodological details for GARIMAX are available in the Supplementary Material.

To capture potential shifts in seasonal peaks, cases were grouped into overlapping three-month intervals (Jan–Mar, Feb–Apr, Mar–May, etc.; see Fig. 2). This flexible approach allowed us to detect recurring seasonal variation even when the peak month varied between years.

Analyses were conducted for the full ALL cohort and separately for BCP-ALL, T-ALL, and the two major BCP-ALL subtypes, HeH and *ETV6::RUNX1*. To assess the specificity of the seasonal pattern observed for ALL, we also examined AML, all brain tumors overall, and medulloblastomas separately as post hoc comparator diagnoses. AML was included because it is diagnosed and managed within the same pediatric hematology/oncology setting as ALL, allowing assessment of whether any pattern might reflect shared diagnostic or healthcare-related factors. CNS tumors were included because their total case number was similar to that of ALL and because they have no clear established etiological association with seasonal infectious exposures. Medulloblastoma was analysed separately because it is the largest malignant pediatric brain tumor subtype and has a case number comparable to the HeH and *ETV6::RUNX1* BCP-ALL subtypes, making it suitable for a similarly informative subtype-specific analysis.

Given the distinct biology and etiology of infant leukemia, we performed a sensitivity analysis restricted to the non-infant ALL cohort aged 1–17 years.

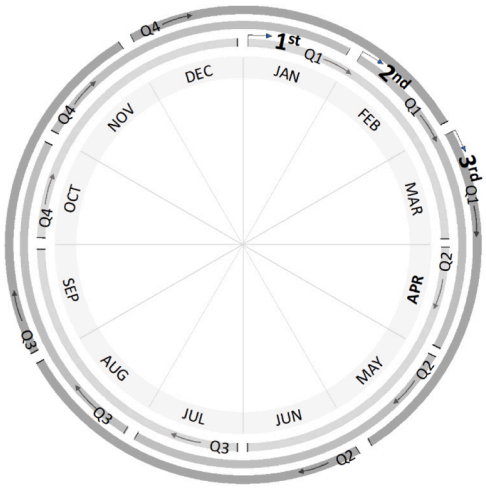

Fig. 2. *Quarter aggregation.* Circle plot illustrates quarters (Q) 1–4 for each of the three quarter types and the months they encompass.

3. Results

A total of 1504 ALL cases were included (1305 BCP-ALL, 175 T-ALL, 24 missing immunophenotype), along with 214 AML, 1367 brain tumor, and 224 medulloblastoma cases identified from the SCCR and NCR (Fig. 1). Among BCP-ALL, 422 cases were HeH and 259 *ETV6::RUNX1*-positive. In the Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL-1992 protocol, only 48% (679/1428) were tested for

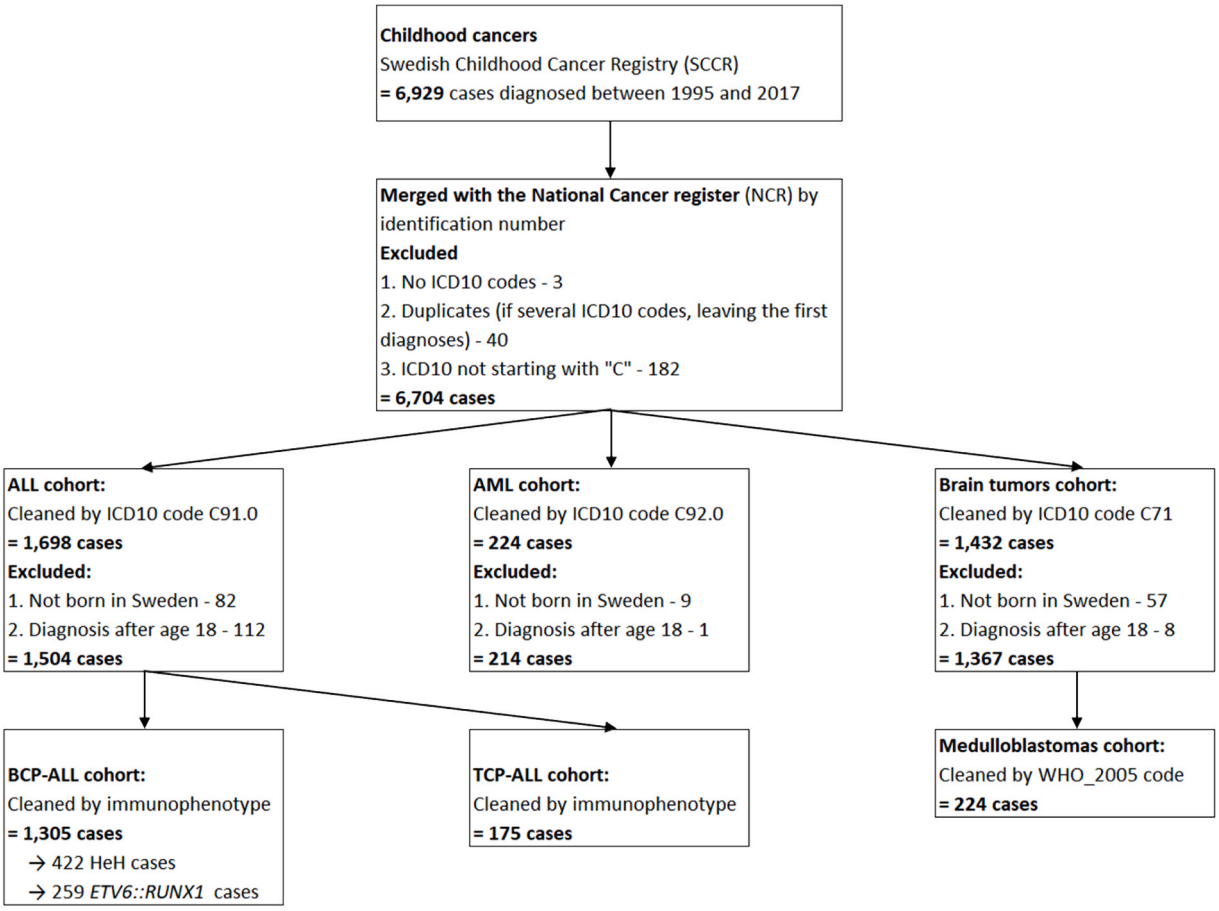

Fig. 1. *Cohort selection.* Flow chart of cohort selection specifying selection criteria and case numbers included and excluded in total, as well as by each subsequent criteria applied.

ETV6::RUNX1, with 25% positivity, consistent with expected frequency. Later NOPHO protocols introduced systematic molecular subtyping. High hyperdiploidy remained stable over time due to detection by conventional cytogenetics [57]. Thus, the lower *ETV6::RUNX1* proportion in 1995–2005 reflects the gradual adoption of molecular diagnostics (FISH, RT-PCR) after its 1994 discovery, not biological differences.

The age distribution of BCP-ALL diagnosis (Fig. 3) showed the expected peak at 2–6 years, while T-ALL was more evenly distributed, with a median diagnosis age of ~9 years, consistent with previous reports. Case distributions by immunophenotype, genetic subtype, year of diagnosis, age, and sex for ALL, and by year, age, and sex for AML, brain tumors, and medulloblastoma, are summarized in Table 1.

Informative seasonal waves were detected across all quarters for the entire ALL cohort. The 95% credible interval for the posterior distribution of the seasonal harmonic function coefficients did not include zero, indicating non-random periodicity. The identified peak quarters were Jul-Sep, Aug-Oct, and Jun-Aug for each quarter type, with August being a common month across all peak periods (Table 2, Supplementary Figure S1).

BCP-ALL and T-ALL immunophenotypes also demonstrated seasonal variation, though not uniformly across all quarter types. For BCP-ALL, the harmonic functions were informative in the first and third quarter types, with peak periods in Jul-Sep and Jun-Aug, respectively. However, the second quarter type did not show informative periodicity for the BCP-ALL cohort (Table 2, Supplementary Figure S2). The months June, July, August, and September were included in these peak periods, with July and August being common to both. For T-ALL, informative seasonal variation was found in the first and second quarter types, with peak quarters in Jul-Sep and Aug-Oct, respectively. The third quarter type did not show informative periodicity for the T-ALL cohort (Table 2, Supplementary Figure S3). The months July, August, September, and October were included in these peak periods, with both August and September overlapping.

Subgroup analysis using the GARIMAX model was conducted on two subgroups of the BCP-ALL cohort: cases with HeH and those with *ETV6::RUNX1* fusion. No informative periodicity was detected in any of the three quarter-types for either subgroup (Table 2, Supplementary Figures S4, S5). Despite the lack of informative periodicity, peak quarters were extracted from the GARIMAX estimates. For the HeH subtype,

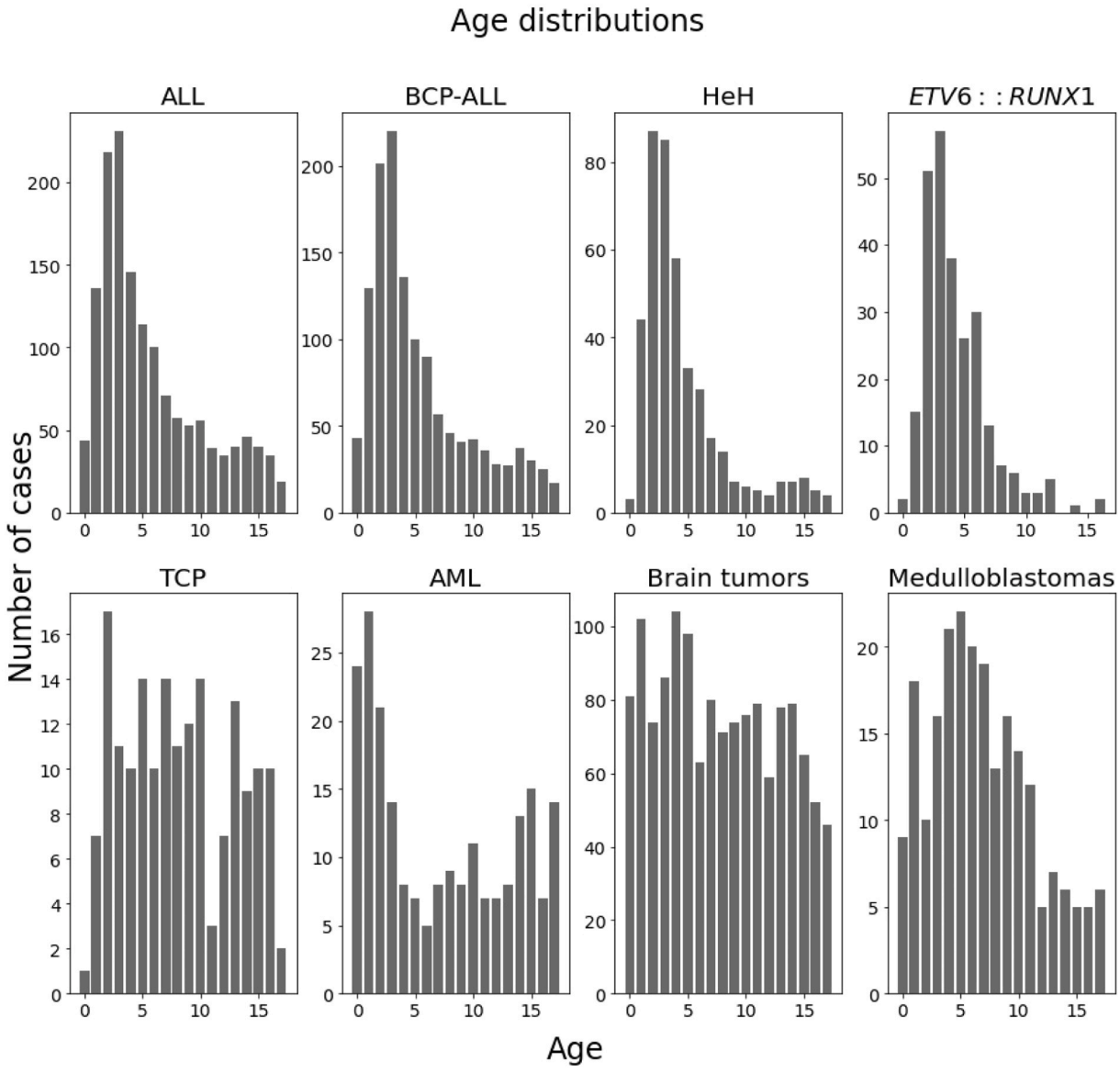

Fig. 3. *Distributions of age at diagnosis for childhood ALL, AML and brain tumors.* The figure illustrates the distribution of age at diagnosis across various childhood cancer types, including ALL, its immunophenotypes (BCP-ALL, TCP-ALL), subtypes of BCP-ALL (HeH and *ETV6::RUNX1*), AML, brain tumors, and medulloblastomas.

Table 1
Patient characteristics of cases diagnosed before 18 years of age by leukemia/tumor type, year of diagnosis, age group, and sex.

	Total ALL cohort	BCP-ALL	HeH subtype	*ETV6::RUNX1*	T-ALL	AML	Brain tumors	Medullo blastomas
All cases	1504	1305	422	259	175	214	1367	224
Year of diagnosis								
1995–2005	746	657	204	89	77	101	679	119
	(49.6)	(50.3)	(48.3)	(34.4)	(44.0)	(47.2)	(49.7)	(53.1)
2006–2017	758	648	218	170	98	113	688	105
	(50.4)	(49.7)	(51.7)	(65.6)	(56.0)	(52.8)	(50.3)	(46.9)
Age at diagnosis								
0	47	43	3	2	1	24	81	9
	(3.1)	(3.3)	(0.7)	(0.8)	(0.6)	(11.2)	(5.9)	(4.0)
1–4	735	686	274	161	45	71	366	65
	(48.9)	(52.6)	(64.9)	(62.2)	(25.7)	(33.2)	(26.8)	(29.0)
5–9	406	334	99	82	61	37	386	90
	(27.0)	(25.6)	(23.5)	(31.7)	(34.9)	(17.3)	(28.2)	(40.3)
10–14	221	170	29	12	46	46	371	44
	(14.7)	(13.0)	(6.9)	(4.5)	(26.3)	(21.5)	(27.2)	(19.6)
15–17	95	72	17	2	22	36	163	16
	(6.3)	(5.5)	(4.0)	(0.8)	(12.5)	(16.8)	(11.9)	(7.1)
Sex								
Male	850	701	220	152	132	105	774	147
	(56.5)	(53.7)	(52.1)	(58.7)	(75.4)	(49.1)	(56.6)	(65.6)
Female	654	604	202	107	43	109	593	77
	(43.5)	(46.3)	(47.9)	(41.3)	(24.6)	(50.9)	(43.4)	(34.4)

Percentage of cohort by column (%).
The model specification (AR/MA lags) was determined using the Bayesian Information Criterion (BIC) score. BIC scores for all tested GARIMAX models are presented in supplementary Table S2. The best GARIMAX specifications for each quarterly series are summarized in supplementary Table S3.

peak quarters were identified in July–September, August–October, and June–August for the first, second, and third quarter types, respectively. In contrast, the *ETV6::RUNX1* fusion-positive subtype showed peak periods in Oct–Dec, Aug–Oct, and Sep–Nov. While the HeH peaks closely matched those of the overall BCP-ALL cohort, the *ETV6::RUNX1* fusion-positive subgroup displayed different patterns.

A manual examination of the monthly absolute number of ALL, BCP-ALL, and T-ALL cases showed that the highest number of ALL cases occurred in August, with 154 cases (10.41%). BCP-ALL also peaked in August, with 134 cases (10.27%), while T-ALL reached maximum incidence in both January and August, with 20 cases (11.43%) each (Table S4).

As a complementary analysis, to evaluate if seasonal variation was specific to ALL, the GARIMAX model was applied to three non-ALL cohorts; AML, all brain tumors combined, and medulloblastomas, to compare the results with those for ALL subtypes, including BCP-ALL, T-ALL, HeH, and *ETV6::RUNX1* fusion-positive. We did not find any informative periodicity in any of the three quarter types analyzed for AML, all brain tumors combined, and medulloblastomas (Supplementary Table S5, Supplementary Figures S6, S7, and S8).

In sensitivity analyses restricted to non-infant ALL, the overall findings remained consistent: BCP-ALL and T-ALL exhibited quarter-specific seasonal variation, whereas no informative seasonality was observed for HeH or *ETV6::RUNX1*-positive cases; detailed results are provided in Supplementary Table S6.

4. Discussion

In this nationwide, population-based Swedish cohort, we applied a GARIMAX time-series model to evaluate seasonal variation in 1504 cases of childhood ALL aged 0–17 years, and compared these patterns with those observed in AML, medulloblastoma, and all brain tumors combined. Our analysis demonstrated consistent evidence of seasonal variation in ALL diagnoses, with peak quarters spanning June-August, July-September, and August-October, with August included in all peak periods. This pattern persisted after stratifying by BCP-ALL and T-ALL immunophenotypes. For BCP-ALL, peaks occurred in June–August and July-September, whereas T-ALL showed peaks in July-September and August–October. In contrast, no seasonal variation was observed for AML, medulloblastoma, or all brain tumors combined. Although the HeH subtype showed peak quarters consistent with the overall ALL pattern, we did not detect statistically informative seasonality in this subgroup. In contrast, the *ETV6::RUNX1*-positive subtype showed non-informative peak periods that did not align with the overall ALL cohort, suggesting potential etiological differences requiring further investigation in larger datasets.

Previous studies of seasonality in childhood ALL show inconsistent results. Of approximately 40 studies, 20 found seasonal variation: 11 reports from four continents and multiple time zones observed summer peaks, five reported winter peaks, and the remaining cohorts found other seasonal patterns. However, only 11/40 studies included more than 1000 cases, and results across these larger cohorts remain inconclusive. While some large studies (Iran, France, US, UK) reported summer peaks [58–61], a nationwide study from South Korea identified a winter peak [62], other large studies from France, US, and UK found no consistent seasonal pattern. Overall, the available evidence does not support a uniform or reproducible seasonal effect in childhood ALL.

Unlike our study, most previous studies analyzed BCP-ALL and T-ALL jointly, without stratification by genetic subtype, potentially obscuring subtype-specific patterns if etiological mechanisms differ between molecular subgroups. Interpretation is further complicated by methodological heterogeneity. A wide range of statistical approaches has been used, including joinpoint regression, the Mardia and Edwards test, Rogers' test, Poisson regression with harmonic functions, and ARIMA models (Supplementary Table S1). These methods differ in their ability to account for temporal trends, overdispersion, and random variation. In contrast, we used GARIMAX specifically to assess seasonal variation while accounting for these limitations. To our knowledge, only one previous study, by Shim et al. [62], applied an advanced time-series approach (ARIMA) and reported a winter peak (Dec–Feb) in ALL diagnoses in South Korea, in contrast to the summer-associated peaks observed in our study.

Our previous observation of space–time clustering of HeH [63] and the reported clustering of *ETV6::RUNX1*-positive ALL [43] motivated subgroup analyses of HeH and *ETV6::RUNX1*-positive BCP-ALL. Although we could not confirm informative seasonal variation in these subgroups, HeH showed peak quarters that aligned with those of BCP-ALL and overall ALL, suggesting that it may contribute to the

Table 2
Summary of statistics for posterior distributions of the coefficients of harmonic functions in ALL, BCP-ALL, T-ALL, HeH, and *ETV6::RUNX1* fusion-positive. The informative harmonic covariate (95% credible interval that does not contain the 0 value) is highlighted in grey color.

Analyzed series	Harmonic Function	Posterior distribution median	95% credible interval for posterior distribution		Peak Quarter
			2.5%	97.5%	
ALL					
1st Qt	Sin wave (β_1)	-0.1090	-0.1805	-0.0366	Jul-Sep
	Cos wave (β_2)	-0.0249	-0.0974	0.0510	
2nd Qt	Sin wave (β_1)	-0.1095	-0.1872	-0.0326	Aug-Oct
	Cos wave (β_2)	-0.0161	-0.0905	0.0590	
3rd Qt	Sin wave (β_1)	-0.0328	-0.1160	0.0498	Jun-Aug
	Cos wave (β_2)	-0.1112	-0.1917	-0.0265	
BCP-ALL					
1st Qt	Sin wave (β_1)	-0.0961	-0.1731	-0.0198	Jul-Sep
	Cos wave (β_2)	-0.0302	-0.1075	0.0492	
2nd Qt	Sin wave (β_1)	-0.0770	-0.1581	0.0034	Aug-Oct
	Cos wave (β_2)	-0.0185	-0.0962	0.0664	
3rd Qt	Sin wave (β_1)	-0.0172	-0.1002	0.0627	Jun-Aug
	Cos wave (β_2)	-0.1118	-0.1936	-0.0290	
T-ALL					
1st Qt	Sin wave (β_1)	-0.1933	-0.3666	-0.0217	Jul-Sep
	Cos wave (β_2)	0.0728	-0.0966	0.2415	
2nd Qt	Sin wave (β_1)	-0.5069	-0.7517	-0.2626	Aug-Oct
	Cos wave (β_2)	-0.0575	-0.2656	0.0473	
3rd Qt	Sin wave (β_1)	-0.2288	-0.4670	0.0169	Jun-Aug
	Cos wave (β_2)	-0.2737	-0.4747	0.0572	
HeH					
1st Qt	Sin wave (β_1)	-0.1374	-0.2822	0.0128	Jul-Sep
	Cos wave (β_2)	-0.0647	-0.2119	0.0767	
2nd Qt	Sin wave (β_1)	-0.0368	-0.1769	0.1038	Aug-Oct
	Cos wave (β_2)	0.0349	-0.1001	0.1747	
3rd Qt	Sin wave (β_1)	-0.0167	-0.1689	0.1341	Jun-Aug
	Cos wave (β_2)	-0.0700	-0.2195	0.0778	
ETV6::RUNX1					
1st Qt	Sin wave (β_1)	0.0198	-0.1638	0.2157	Oct-Dec
	Cos wave (β_2)	0.1524	-0.0309	0.3348	
2nd Qt	Sin wave (β_1)	-0.1371	-0.3346	0.1025	Aug-Oct
	Cos wave (β_2)	0.1036	-0.0658	0.2204	
3rd Qt	Sin wave (β_1)	-0.1555	-0.3602	0.0437	Sep-Nov
	Cos wave (β_2)	-0.1015	-0.3087	0.1036	

observed seasonal pattern. In contrast, *ETV6::RUNX1*-positive ALL showed different peak quarters, suggesting a distinct pattern. Future pooled studies of genetic subgroups may help clarify subtype-specific etiologies. Similar results were obtained in a sensitivity analysis restricted to children aged 1–17 years.

The heterogeneity in reported seasonal patterns likely reflects variation in study design and population characteristics. Differences in cohort size, study period, definition of seasonality, case ascertainment, registration practices, and healthcare utilization may all influence findings. Population factors such as age, sex, parental age, genetic background, ethnicity, socioeconomic conditions, and subtype composition may also contribute. In addition, variation in the latency from preleukemia to overt disease, which may differ by subtype, could obscure underlying seasonal effects.

Environmental and regional factors are also important. Differences in time zone, climate, daylight exposure, solar ultraviolet radiation, and temperature, including exposures during early pregnancy, may influence both leukemogenesis. Behavioral and societal factors, such as daycare, school attendance, travel, holidays, and seasonal social mixing shape infectious exposure dynamics, including the timing and intensity of outbreaks, susceptibility to non-endemic pathogens, and infections occurring in utero or during early childhood. Differences in microbial early-life exposures that influences maturation of the child's immune system may also vary seasonally [16–40,59,64]

Furthermore, maternal and environmental exposures - including diet, hormonal contraception, pesticides, household chemicals, air pollution, and ionizing radiation, have all been implicated as potential risk modifiers for leukemia [16–35].

Evidence suggests that the influence of these factors may vary between molecular BCP-ALL subtypes [18,41–43]. For example, experimental studies in genetically predisposed transgenic mouse models carrying the *ETV6::RUNX1* fusion or Pax5+/− genotype show that BCP-ALL develops only after exposure to common infections, albeit with incomplete penetrance, supporting a causal role for infections in leukemia development for these subtypes [65,66]. Other examples are reported associations between household paint exposure and KMT2A-rearranged, HeH or *ETV6::RUNX1*-positive ALL, as well as pesticide exposure and HeH or *ETV6::RUNX1*-positive ALL [67,68]. Together, these factors highlight the challenges of comparing results across diverse geographic and climatic settings, where both geography, genetic background, environmental exposures and human behaviors vary. [19,23,59–64].

We observed summer-associated peaks in ALL, consistent with a potential role for infectious exposures. However, our data do not allow firm conclusions, and other factors, such as recently reported associations with ambient temperature during early pregnancy, may also contribute. Space–time clustering in ALL, also including HeH and *ETV6::RUNX1*-positive subtypes supports the hypothesis of infectious exposure heterogeneity, but clustering may also reflect environmental variables [43,63,69]. Sweden's long summer break (mid-June to mid-August) may possibly create a "lockdown effect", with fewer ALL cases initiating during the vacation period and a subsequent increase after children return to daycare/school, potentially reflecting changes in infectious exposure. We considered the possibility that delays in diagnosis, either by doctors or parents, during summer vacation could explain our findings. This aligns with reports of lower detection rates and higher mortality in adult cancer patients diagnosed during Sweden's holiday season [70]. To investigate the possibility of a "doctor's delay" in diagnosing ALL, we conducted GARIMAX analyses on comparison groups, including patients with AML, all brain tumors combined, and medulloblastomas. None of the comparison groups, showed informative seasonal variation, and their peak quarters did not coincide with the seasonal peaks observed for ALL. While we cannot completely rule out a diagnostic delay in ALL, the absence of seasonal variation in the comparison groups, together with the typically acute and rapidly progressing symptoms of ALL at diagnosis, makes this explanation less likely.

5. Limitations

Although seasonal variation suggests a potential role for infectious exposures, our study cannot robustly assess associations with specific pathogens as we lack suitable data on microbial infection waves from primary care and other relevant sources, and the underlying mechanisms therefore remain speculative.

Registry-based infection diagnoses based on health data from specialist care registers are an imperfect proxy, as many infections are managed in primary care and may be underreported in specialist registers, and temporal changes in healthcare utilization, coding, and testing may affect incidence [71]. Furthermore, the GARIMAX methodology cannot reliably estimate the induction period between infection peaks and leukemia onset. Identifying specific infectious triggers will require more detailed microbiological or surveillance data. The GARIMAX methodology is based on aggregated time-series data and does not allow adjustment for individual-level covariates.

6. Strengths

A key strength of the study is the use of GARIMAX, a robust model for seasonal count data that captures yearly variation while accounting for overdispersion through a negative binomial framework. Aggregating cases by quarter also helped reduce the influence of short-term fluctuations, such as seasonal viral peaks. Another strength is the use of population-based national cancer register data together with detailed SCCR data, which enabled analyses of genetic subtypes and comparisons with other childhood cancers, including AML, solid tumors, and brain tumors.

7. Conclusions

We demonstrate evidence of seasonal variation in childhood ALL, with consistent summer-associated peaks across immunophenotypes. In contrast, no clear seasonal pattern was observed for AML or brain tumors, suggesting that seasonality may be specific to ALL. Subtype-specific analyses indicate potential etiological heterogeneity, although larger studies are required to confirm these findings. Future research integrating genetic, environmental, and infectious data across large cohorts will be essential to elucidate the mechanisms underlying seasonal variation in childhood leukemia.

CRediT authorship contribution statement

Jan Albert: Writing – review & editing, Resources, Investigation, Formal analysis. **Ann Nordgren:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Benedicte Bang:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Data curation. **Niklas Engsner:** Writing – review & editing, Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **Rebecka Jörnsten:** Writing – review & editing, Software, Methodology, Formal analysis, Data curation. **Claes Strannegård:** Writing – review & editing, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gleb Bychkov:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation. **Anna Skarin Nordenvall:** Writing – review & editing, Data curation. **Nikolas Herold:** Writing – review & editing, Investigation. **Giorgio Tettamanti:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Mats Marshall Heyman:** Writing – review & editing, Resources, Data curation. **Fulya Taylan:** Writing – review & editing, Validation, Investigation, Data curation. **Emeli Pontén:** Writing – review & editing, Investigation.

Ethics approval

This study was approved by the Regional Ethical Review Board in Stockholm (Dnr 2023–06901–01) and was conducted in accordance with the Declaration of Helsinki.

Author contribution

AN, CS, NE, RJ, GB, and BB designed the study. NE, GB, CS, and AN analyzed the data. GB, NE, AN, CS, RJ, and BB interpreted the data. GB performed the GARIMAX analysis. GB, BB, and AN reviewed the literature; AN, MMH, NH, JA, EP, FT, and BB contributed medical and genetic knowledge. GT and ASN contributed to epidemiology and

statistical analysis. GB and NE prepared the figures. GB and AN wrote the first draft of the manuscript. All authors contributed to the data interpretation, revised the manuscript, and approved the final version.

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Declaration of Competing Interest

All authors state that they have no conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2026.103069.

Data availability

This article only includes summarized data of this study. The raw data is available from the corresponding author upon reasonable request.

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