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Socioeconomic status and event free survival in pediatric acute lymphoblastic leukemia: A population-based cohort study

Sumit Gupta[a,*], Rinku Sutradhar[b,c], Astrid Guttmann[b,d,e], Lillian Sung[a,e], Jason D. Pole[f]

[a] Division of Haematology/Oncology, Department of Paediatrics and Program in Child Health Evaluative Sciences, The Hospital for Sick Children, 555 University Avenue, Toronto, Canada M5G 1X8
[b] Institute for Clinical Evaluative Sciences, G1 06, 2075 Bayview Avenue, Toronto, Canada M4N 3M5
[c] Dalla Lana School of Public Health, University of Toronto, 6th floor, 155 College Street, Toronto, Canada M5T 3M7
[d] Division of Paediatric Medicine, Department of Paediatrics, Hospital for Sick Children, 555 University Avenue, Toronto, Canada M5G 1X8
[e] Institute of Health Policy, Management and Evaluation, University of Toronto, Suite 425, 155 College Street, Toronto, Canada M5T 3M6
[f] Pediatric Oncology Group of Ontario, Suite 1014, 480 University Avenue, Toronto, Canada M5G 1V2

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ABSTRACT

The impact of socioeconomic status (SES) upon childhood cancer outcomes has not been extensively examined. Our objective was to determine the association between SES and event-free survival (EFS) among children with acute lymphoblastic leukemia (ALL) diagnosed in Ontario, Canada from 1995–2011 ($N = 1541$) using Cox proportional hazards. Neither neighborhood-level median income quintile, distance from tertiary center, or rural residence significantly predicted EFS in the context of a universal healthcare system. Immigrant children experienced significantly superior EFS; confounding by ethnicity could not be ruled out. Confirmatory studies using additional individual-level SES variables are warranted.

1. Introduction

Remarkable progress has been made in pediatric acute lymphoblastic leukemia (ALL), with event-free survival (EFS) now approximating 85% [1,2]. However, relapsed ALL still represents the fourth most common malignancy; most of these children die as a consequence of their disease [3]. Current efforts to ascertain the cause of relapse in these children have focused on multiple biologic factors including leukemia genetic lesions or host polymorphisms [4,5].

Relative to these biologic variables, the potential role of socioeconomic status (SES) has been poorly studied despite documented impact on adult cancer outcomes [6]. Several authors have theorized that SES may also impact childhood cancer outcomes through multiple mechanisms [7–11]. For example, low rates of therapy compliance in ALL have been demonstrated in single mother households and linked to higher relapse risk [12].

If lower socioeconomic status is directly correlated with worse survival, targeted interventions would be warranted in order to further improve outcomes. We therefore aimed to determine whether two measures of SES (neighborhood income quintile, immigrant status) were associated with 5-year EFS among children with ALL in a jurisdiction with universal healthcare coverage. As a secondary objective, we also aimed to determine whether potential barriers to healthcare access (rural residence, distance from a tertiary pediatric cancer center) were associated with 5-year EFS.

2. Material and methods

2.1. Study population and setting

This study included all Ontario, Canada residents diagnosed with primary ALL from 1995–2011, <18 years of age at diagnosis, and treated at one of the five tertiary pediatric oncology centers. Non-residents were excluded, as were cases of secondary ALL. Patients with mature B-ALL (Burkitt's leukemia) were also excluded given their different treatment and prognosticators. Date of diagnosis was defined as that of the procedure leading to the definitive ALL diagnosis. Healthcare in Ontario consists of a

Abbreviations: CIC, Citizenship and Immigration Canada; DAD, Discharge Abstract Database; EA/DA, enumeration/dissemination area; ICES, Institute for Clinical Evaluative Sciences; OHIP, Ontario Health Insurance Program; POGONIS, Pediatric Oncology Group of Ontario Networked Information System; RPDB, Registered Persons Database; SES, socioeconomic status; SMN, second malignant neoplasms; WBC, white blood cell.

* Corresponding author. Tel.: +1 416 813 7654x201681; fax: +1 416 813 5327.
E-mail address: sumit.gupta@sickkids.ca (S. Gupta).

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Table 1
Study data sources.

Data source	Data type	Study use
POGONIS	Childhood Cancer Registry	Cohort identification and demographics Date of diagnosis Outcome data Treatment protocol name
DAD	Hospitalizations	Outcome data
OHIP	Physician Claims	Outcome data
Canadian Census	Small-area aggregate data	Median neighborhood income quintile
RPDB	Demographic data	Outcome data
CIC Database	Federal Immigration Registry	Immigrant status
Chart Abstraction	Clinical Information	Disease risk measures

DAD, Discharge Abstract Database; ED, Emergency Department; NACRS, National Ambulatory Care Reporting System; OHIP, Ontario Health Insurance Plan; POGONIS, Pediatric Oncology Group of Ontario Networked Information System; RPDB, Registered Persons Data Base.

single-payer, universal insurance system in which all medically necessary physician and hospital services are funded by the government. Ancillary costs (e.g. outpatient medications) are covered through either private insurance or government programs for specific disadvantaged populations; not all families lacking private insurance qualify for these programs. Psychosocial support is provided by social workers, while specialized nurses provide support in the home, school and community settings. Most children were treated with contemporaneous protocols designed by cooperative groups [13–16], though some earlier patients were treated using local protocols.

2.2. Data sources

Table 1 lists the data sources and their specific use in this study. Cohort patients were identified through the Pediatric Oncology Group of Ontario Networked Information System (POGONIS), a population-based registry that prospectively captures all cases of pediatric cancer diagnosed at tertiary pediatric oncology centers [17].

Several health services databases housed at the Institute for Clinical Evaluative Sciences (ICES) were accessed in order to obtain information about deaths, date of last contact and relapses beyond the childhood period. These databases included the Discharge Abstract Database (DAD – hospital admission records), and the Ontario Health Insurance Plan Claims Database (OHIP – physician services). In addition, the Registered Persons Data Base (RPDB) comprises basic demographic data of all Ontarians eligible for insured services. In order to identify immigrants, we accessed the Citizenship and Immigration Canada (CIC) database, which is a federal registry of all landed immigrants since 1986. A total of 85.8% of individuals in the CIC were successfully linked to other ICES databases. While the CIC does not contain data on race or ethnicity, the country from which emigration took place is available. All data is linked through unique individual identifiers based on scrambled health card numbers. In addition, small-area level aggregate data collected by the Canadian Census, conducted every five years, were available. Finally, specific measures of disease risk were obtained on a portion of the cohort via chart abstraction (see below).

2.3. Outcome measures

Dates of death were obtained from the POGONIS and RPDB, as were date of relapse or second malignant neoplasms (SMN – POGONIS), and date of last contact with the healthcare system (RPDB – used as a censoring time point). Relapses or SMNs occurring after transfer to adult centers were identified using health services data to identify healthcare records with relevant procedure codes (see Supplemental Data).

2.4. Potential predictors

Potential predictor variables were based on previous literature and data availability [11,18–21], including demographic (age at diagnosis, gender, diagnostic time period), socioeconomic, health care access and disease risk factors. Age was categorized as <1 year vs. 1 to <10 vs. 10–17 in keeping with current National Cancer Institute risk classifications [18]. Diagnostic time period was defined as early (1995–2000) vs. middle (2001–2005) vs. late (2006–2011).

The primary socioeconomic variable was neighborhood median income quintile. The smallest area for which census information is publically available is the enumeration area or dissemination area (EA/DA), each containing 400–700 persons. 20% of households within each EA/DA are sampled and aggregated to calculate median household income. Adjustments for household size are made to calculate per single-person equivalents. Quintiles of adjusted median neighborhood income are constructed within defined metropolitan or agglomeration areas [22,23]. Patients were linked to EA/DA of the census closest to the date of diagnosis using postal code at diagnosis.

Table 2
Study cohort demographics.

	N available	Median (IQR)	*N* (%)
Demographic variables			
Age (years)	1541	4.6 (3.0–8.5)	
1 to <10			1194 (77.5)
10–17			303 (19.7)
<1			44 (2.9)
Gender	1541		
Female			678 (44.0)
Male			863 (56.0)
Time period	1541		
Early (1995–2000)			517 (33.6)
Middle (2001–2005)			435 (28.2)
Late (2006–2011)			589 (38.2)
Disease risk variables			
Risk strata[a]	1501		
Standard risk			702 (46.8)
High risk			799 (53.2)
WBC ($\times 10^9$/L)	779	9.3 (4.0–32.3)	
<50			633 (81.3)
50 to <100			64 (8.2)
≥100			82 (10.5)
Lineage	788		
B			716 (90.9)
T			72 (9.1)
Cytogenetics[b]	758		
Low risk			401 (52.9)
Standard risk			311 (41.0)
High risk			46 (6.1)
Socioeconomic variables			
Neighborhood median income quintile	1539		
Q1 (lowest)			285 (18.5)
Q2			304 (19.8)
Q3			324 (21.1)
Q4			342 (22.2)
Q5 (highest)			284 (18.5)
Immigrant	1541		
No			1476 (95.8)
Yes			65 (4.2)
Healthcare access variables			
Distance from tertiary center (km)	1541	29.2 (13.9–61.4)	
Short[b]			1155 (75.0)
Long[b]			386 (25.0)
Rurality	1541		
Urban			1365 (88.6)
Rural			176 (11.4)

IQR, interquartile range; *N*, number; WBC, white blood cell count.
[a] Based on treatment protocol name.
[b] See text for definitions.

Immigrant status was determined via linkage with the CIC database, which identified all children born outside of Canada. Country of emigration was also determined. Additionally, two measures of potential healthcare access were examined. Rurality was defined by postal code at diagnosis, using the Rurality Index for Ontario 2004, which is based on factors including population size and the presence of a hospital [24]. This score has been used for health resource allocation planning [24]. Distance from the closest tertiary pediatric center was categorized into short versus long using the 75th percentile (61.41 km).

2.5. Disease risk variables

Risk stratification schemas based upon age, white blood cell count at presentation (WBC), lineage (B vs. T), leukemia cytogenetics and response to therapy are used to guide treatment intensity [18]. Despite the importance of including these variables in prognostic models, they are generally not available on a population-wide basis. Two strategies were therefore pursued. First, our previous work has shown that risk algorithms based on treatment protocol name approximated algorithms using specific disease biology variables [25]. As POGONIS collects treatment protocol, our primary disease risk measure was derived using this algorithm (standard vs. high risk).

Secondly, specific disease risk variables (WBC, lineage, cytogenetics) were obtained through chart abstraction of a portion of the study cohort: children treated at the Hospital for Sick Children after June 2000 and all children treated at