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Access to Hematopoietic Stem Cell Transplantation among Pediatric Patients with Acute Lymphoblastic Leukemia: A Population-Based Analysis

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A B S T R A C T

Access to hematopoietic stem cell transplantation (HSCT) in pediatric acute lymphoblastic leukemia (ALL) primarily depends on disease-related factors but may be influenced by social and economic determinants. We included all children aged < 15 years with newly diagnosed ALL in Canada between 2001 and 2018 using the Cancer in Young People in Canada national registry. We examined factors potentially associated with the likelihood of receiving HSCT using univariate and multivariable logistic regression models. A total of 3992 patients with newly diagnosed ALL were included. Three hundred twenty-five (8.1%) received an HSCT and formed the transplant cohort. In multivariable analysis factors independently associated with an increased odds of receiving HSCT were male sex (odds ratio [OR], 1.42; 95% confidence interval [CI], 1.05 to 1.93), initial WBC $\geq 50{,}000 \times 10^9$/L (OR, 1.58; 95% CI, 1.09 to 2.28), mixed phenotype acute leukemia relative to B-precursor ALL (OR, 34.32; 95% CI, 16.64 to 70.79), T cell relative to B-precursor ALL (OR, 1.77; 95% CI, 1.07 to 2.91), unfavorable relative to standard cytogenetics (OR, 3.96; 95% CI, 2.56 to 6.12), and relapse before HSCT (OR, 32.77; 95%, 23.89 to 44.96). No association was found between race, neighborhood income quintile or region at diagnosis, and receipt of HSCT. Diagnosis at an HSCT treating center (OR, 1.51; 95% CI, 1.09 to 2.09) and residential distance from the ALL treating center (OR, 1.84 for ≥300 km compared with <100 km; 95% CI, 1.17 to 2.91) were associated with higher odds of receiving HSCT. In a publically funded healthcare system, children with ALL had equitable access to HSCT, which was largely governed by biologic disease-related factors. Patients diagnosed at an HSCT performing center and patients who live farthest away from their treatment center had higher odds of receiving HSCT, although the effect was small, possibly suggesting preferential referral to HSCT for some patients.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a resource-intensive and costly procedure that is only offered at certain specialized centers. The use of HSCT as curative therapy has increased worldwide but has been concentrated among developed countries and those with transplant donor infrastructures [1]. Differential access to HSCT has been reported in many countries within North America, the United Kingdom, and Europe and may be influenced by multiple factors, including disease-related factors, patient factors, donor availability, and sociodemographic, economic, and geographic factors [2–4]. Disparities in access to HSCT have been described mostly in adults, citing differences by age, gender, race, and insurance status [2,5–10].

Among pediatric patients with acute lymphoblastic leukemia (ALL), the use of HSCT is typically reserved for those with high-risk features or relapsed disease, situations in which the

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expected outcomes of HSCT are superior when compared with chemotherapy alone [11,12]. Both the American Society for Blood and Marrow Transplantation and the European Society for Blood and Marrow Transplantation have produced expert-guided consensus documents outlining recommendations for HSCT in pediatric ALL, which largely govern referral practices for HSCT [13,14]. Despite well-established indications, HSCT practices are also guided by clinical trial consortia, which may introduce center variability.

The literature examining access to HSCT among children is scant and often the subject of subgroup analysis from larger adult studies [5–7]. Furthermore, these studies do not incorporate risk factors present at the time of ALL diagnosis. Finally, little work has been performed within a publically funded healthcare system at a population level.

The Cancer in Young People in Canada (CYP-C) national registry was established in 2009 to collect population-level data on all new malignant diagnoses treated at the 17 Canadian pediatric tertiary care centers. Universal access to healthcare is mandated federally but administered by individual provinces and territories. Canada is a geographically vast country with a diverse mix of races, operating under a publically funded healthcare system. These unique attributes allow us to examine questions of healthcare access independent of individual insurance status, a bias evident in other countries and previous studies. Our objectives were to determine whether receipt of HSCT is independently associated with sociodemographic and regional-geographic factors.

METHODS

Study Population

All children with newly diagnosed ALL, including those with precursor B cell ALL, precursor T cell ALL, mixed phenotypic acute leukemia (MPAL), and other types of precursor ALL (International Classification of Diseases for Oncology M codes 9835-9837, 9805, 9808, 9809) in Canada were included. Patients were less than 15 years of age at diagnosis, diagnosed between January 1, 2001 and June 11, 2018, and treated at 1 of the 17 pediatric oncology centers in Canada. We excluded patients whose ALL diagnosis followed a previous malignancy diagnosis and those who had received a prior solid organ or HSCT.

Data Source

We used the CYP-C database, which is a population-based registry that includes all children (<15 years old) with cancer diagnosed and treated at 1 of the 17 tertiary pediatric oncology centers in Canada. CYP-C is a collaboration between the federal Public Health Agency of Canada, the C17 Council, and the Canadian Partnership against Cancer. CYP-C includes all pediatric cancers diagnosed at pediatric tertiary care institutions since 2001 and captures outcomes for 5 years after diagnosis or an eligible second malignancy. Data are collected and submitted to CYP-C in 2 ways. For the 5 Ontario centers data are transferred to CYP-C via the Pediatric Oncology Group of Ontario Networked Information System, which is a provincial population-based registry that predates CYP-C. The 12 centers outside of Ontario enter data directly into CYP-C. Elements captured by both databases include demographic variables (sex, date of birth, postal code, and race), diagnostic details, times to diagnosis and treatment, treatment plan details, and outcomes such as relapse, second malignancy, and death. The CYP-C program achieves high-quality data through a community of practice composed of each site's data manager, monthly review teleconferences, and annual face-to-face training combined with site audits.

Primary Outcome and Potential Risk Factors

The primary outcome was receipt of first HSCT. Four categories of potential factors were associated with receipt of HSCT. First, demographic features were sex, age at ALL diagnosis (<1 year, 1 to <10 years, and 10 to 14 years), race (white versus nonwhite), and ALL diagnostic period (2001 to 2005, 2006 to 2009, 2010 to 2013, and 2014 to 2018). Second, leukemia features comprised initial WBC count ($\geq 50 \times 10^9$/L versus $<50 \times 10^9$/L), ALL immunophenotype (B-precursor, T cell, and MPAL), cytogenetic classification (favorable, standard, and unfavorable), and relapse before receiving HSCT. The third factor was ALL treatment center characteristics: region of treating center (West, Central, and East) and whether the treating center also performs HSCT. Fourth, socioeconomic features included distance in kilometers (km) to the ALL treatment center and neighborhood income quintile.

Cytogenetic groups were defined as favorable (double trisomies of chromosome 4 and 10 or t(12;21)), unfavorable (MLL rearrangement, t(9;22) Philadelphia chromosome, iAMP21, or near haploidy/hypodiploid), and standard (ie, all others) [15]. The region of ALL treatment center was categorized as West (British Columbia, Alberta, Saskatchewan, and Manitoba), Central (Ontario), and East (Quebec and the Atlantic provinces).

We also examined if the patient received ALL treatment at a center that also performs HSCT. Six of the 17 pediatric cancer centers perform pediatric HSCT. Residential postal codes at ALL diagnosis were used to determine distance to the ALL treatment institution and stratified into 100-km increments, with the last category ≥300 km. Postal codes were also used to determine area-level socioeconomic status. Full 6-digit postal codes were available for all provinces except British Columbia, in which 3-digit postal codes were available. We used the Statistics Canada Postal Code Conversion File software (PCCF+, version 4J) to link the postal code at diagnosis to the Canadian 2006 census dissemination area. Dissemination areas are the smallest area unit defined by Statistics Canada and include between 400 and 700 persons. Using this linkage, we determined income quintiles that adjust for household size and regional differences [16–18].

Statistical Analysis

Among children with newly diagnosed ALL, we described those who did and did not receive first HSCT and compared features using the chi-square test or Fisher's exact test. Continuous variables were compared using the Wilcoxon rank sum test. We evaluated the variables associated with receiving HSCT using univariate and multivariable logistic regression models, and associations were estimated using odds ratios (ORs) with 95% confidence intervals (CIs). Multivariable models included all evaluated factors. Because of the high proportion of missing data for some covariates, missing data were analyzed as a separate category in both univariate and multivariable analysis to determine if missing data had any effect on the final model. As mandated by the Public Health Agency of Canada, cell sizes less than 5 were suppressed for privacy reasons and random rounding to the nearest 5 was used, where indicated.

Statistical significance was defined as $P < .05$. Statistical analysis was conducted using the SAS statistical program (SAS-PC, version 9.4; SAS Institute Inc., Cary, NC).

RESULTS

Among 4011 patients with ALL, 19 patients were excluded who had a second diagnosis of ALL (n = 17) and a prior solid organ transplant (n = 2). Overall, 3992 patients with newly diagnosed ALL were included, with 325 patients (8.1%) receiving HSCT. Table 1 illustrates the features of those who did and did not receive HSCT and the proportion receiving HSCT by stratum. Factors significantly associated with receipt of HSCT were sex, age at diagnosis, initial WBC count at ALL diagnosis, immunophenotype, cytogenetics, diagnostic period, relapse before HSCT, and distance from treating center.

Figure 1 illustrates the percentage of patients with ALL receiving HSCT stratified by distance from the patient's home address to the treating ALL center (<100, 100 to <200, 200 to <300, and ≥300 km). Among the entire ALL cohort, 74.6% lived within 100 km of their pediatric cancer treatment center, and of these 8.0% received HSCT, similar to the overall baseline rate of HSCT. Although only 8.3% of the entire cohort lived ≥ 300 km away from their treatment center, 13.3% of these patients received HSCT ($P = .001$; Table 1). The proportion of HSCT procedures performed in patients before and after relapse was similar across the distance categories ($P = .72$).

Figure 2 describes the timing of HSCT in relation to relapse. Because of small cell sizes, numbers were randomly rounded to the nearest 5 and cell sizes less than 5 suppressed. Of the 325 patients who received HSCT, 135 underwent the procedure before any relapse (41.5%). Conversely, 170 patients underwent a first HSCT after 1 relapse, whereas 20 and <5 patients underwent a first HSCT after 2 and 3 relapses, respectively. HSCT-naïve relapses (relapses without a prior HSCT) after first, second, and third relapse were treated with HSCT in 170 of 190 (89.5%), 20 of 20 (100%), and <5 of <5 (100%) patients, respectively.

Table 1
Characteristics of the Study Population Stratified by Receipt of HSCT

Characteristics	Overall Cohort		Did Not Receive HSCT		Received HSCT		Percent Received HSCT	*P*
	(n = 3992)		(n = 3667)		(n = 325)			
	No. of Cases	Percent	No. of Cases	Percent	No. of Cases	Percent		
Sex								.004
Female	1744	43.7	1627	44.4	117	36.0	6.71	
Male	2248	56.3	2040	55.6	208	64.0	9.25	
Age at diagnosis								<.001
<1 yr	123	3.1	85	2.3	38	11.7	30.89	
1 to <10 yr	3224	80.8	3012	82.1	212	65.2	6.58	
10-14 yr	645	16.2	570	15.5	75	23.1	11.63	
Race								.550
White	2413	60.45	2209	60.2	204	62.8	8.45	
Nonwhite	983	24.6	911	24.8	72	22.15	7.32	
Not available	596	14.9	547	14.9	49	15.1	8.22	
Initial WBC count $\times 10^9$/L								<.001
<50,000	2569	64.35	2423	66.1	146	44.9	5.68	
≥50,000	682	17.1	581	15.8	101	31.1	14.81	
Missing	741	18.6	663	18.1	78	24.0	10.53	
Immunophenotype								<.001
B-precursor	2746	68.8	2570	70.1	176	54.15	6.41	
Mixed phenotype	44	1.1	20	.55	24	7.4	54.55	
T cell	324	8.1	283	7.7	41	12.6	12.65	
Missing	878	22.0	794	21.65	84	25.85	9.57	
Cytogenetics*								<.001
Favorable	1046	26.2	1021	27.8	25	7.7	2.39	
Standard	2619	65.6	2387	65.1	232	71.4	8.86	
Unfavorable	327	8.2	259	7.1	68	20.9	20.80	
Diagnostic period								<.001
2001-2005	1125	28.2	1001	27.3	124	38.15	11.02	
2006-2009	933	23.4	856	23.3	77	23.7	8.25	
2010-2013	1045	26.2	959	26.15	86	26.5	8.23	
2014-2018	889	22.3	851	23.2	38	11.7	4.27	
Relapse before HSCT								<.001
Yes	350	8.8	160	4.4	190	58.5	54.29	
No	3642	91.2	3507	95.6	135	41.5	3.71	
Region of treating center†								.130
West	1122	28.2	1038	28.4	84	25.85	7.49	
Central	1794	45.1	1630	44.7	164	50.5	9.14	
East	1059	26.6	982	26.9	77	23.7	7.27	
Diagnosis at HSCT center								.241
Yes	2421	60.65	2214	60.4	207	63.7	8.55	
No	1571	39.35	1453	39.6	118	36.3	7.51	
Distance from treating center‡								.001
0 to <100 km	2929	74.5	2696	74.6	233	73.0	7.95	
100 to <200 km	454	11.55	425	11.8	29	9.1	6.39	
200 to <300 km	201	5.1	190	5.3	11	3.45	5.47	
≥300 km	347	8.8	301	8.3	46	14.4	13.26	
Neighborhood income quintile								.093
1 (lowest)	739	18.5	668	18.2	71	21.8	9.61	
2	762	19.1	707	19.3	55	16.9	7.22	
3	817	20.5	752	20.5	65	20.0	7.96	
4	818	20.5	766	20.9	52	16.0	6.36	
5 (highest)	809	20.3	733	20.0	76	23.4	9.39	
Missing	47	1.2	41	1.1	6	1.8	12.77	

* Cytogenetic category defined as favorable (double trisomies of chromosome 4 and 10, t(12;21)), unfavorable (MLL rearrangement, t(9;22) Philadelphia chromosome, iAMP21, near haploidy/hypodiploid), and standard (all others).
† Region defined as West (British Columbia, Alberta, Saskatchewan, and Manitoba), Central (Ontario), and East (Quebec and Atlantic Provinces) (missing n = 17).
‡ Missing n = 61.

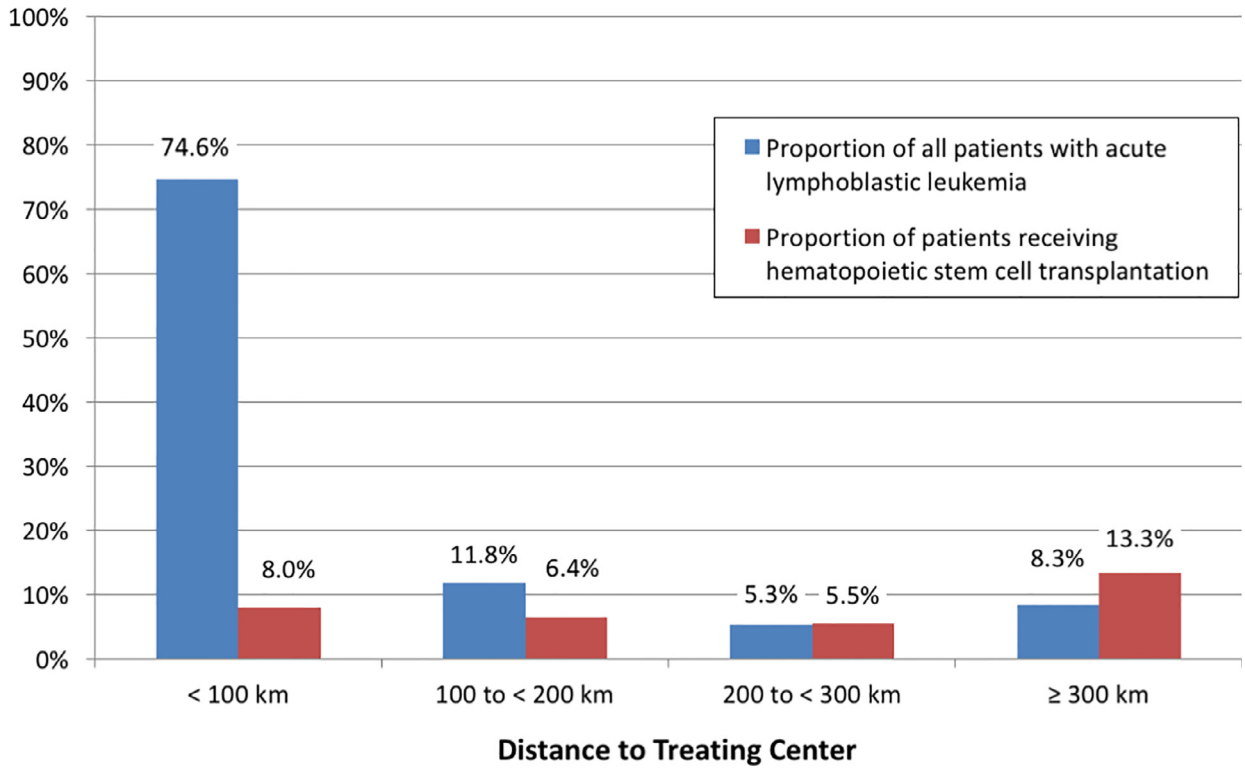

Figure 1. Proportion of patients receiving HSCT by distance to treating center.

Of the 3992 ALL patients, 2421 (60.6%) were diagnosed at an HSCT center and 1571 (39.4%) at a center that does not perform HSCT procedures. For those who received HSCT before relapse, the length of time from ALL diagnosis to receipt of HSCT did not differ between those who were diagnosed at an HSCT center versus a non-HSCT center (median, 152 days [interquartile range, 108 to 202] versus 177 days [interquartile range, 140 to 222], respectively; $P = .086$). Among those who received HSCT after first relapse, there was also no difference in time from relapse date to HSCT for those diagnosed at an HSCT center (median, 134 days; interquartile range, 112 to 153) versus those at a non-HSCT center (median, 141 days; interquartile range, 121 to 171; $P = .205$).

Univariate and Multivariable Analysis

Table 2 shows that in univariate analysis the following factors were associated with receiving an HSCT: male sex, age group, initial WBC $\geq 50{,}000 \times 10^9$/L, immunophenotype, cytogenetics, relapse before HSCT, distance from the treating ALL center, and diagnostic period. Neighborhood quintile was not significantly associated with receipt of HSCT.

In multivariable analysis, independent factors significantly associated with an increased odds of HSCT were as follows: male sex (OR, 1.42; 95% CI, 1.05 to 1.93; $P = .022$), initial WBC count $\geq 50{,}000 \times 10^9$/L (OR, 1.58; 95% CI, 1.09 to 2.28; $P = .015$), MPAL relative to B-precursor ALL (OR, 34.32; 95% CI, 16.635 to 70.79; $P < .0001$), T cell relative to B-precursor ALL

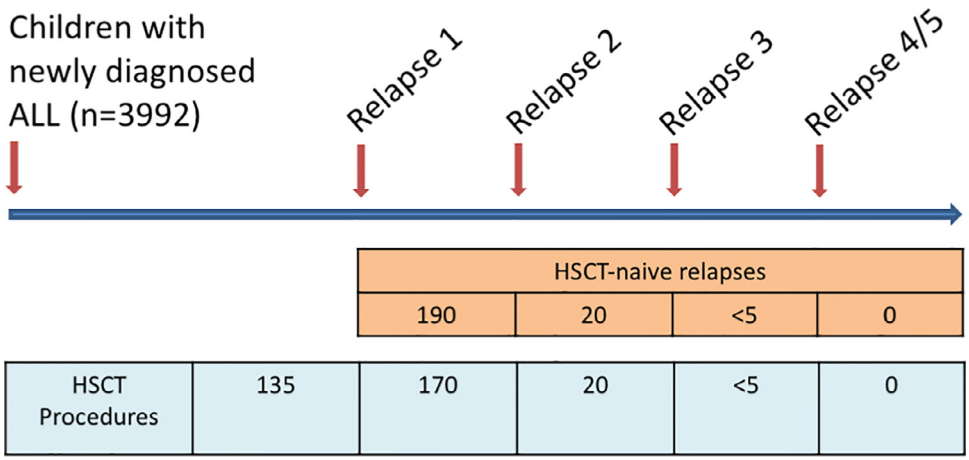

Figure 2. Timing of HSCT relative to relapse. HSCT-naïve relapses represent the number of relapses that have occurred without a prior HSCT. Random rounding for privacy reasons. Frequency counts less than 5 are suppressed.

Table 2
Univariate and Multivariable Model of Factors associated with HSCT in ALL

Variable	Univariate				Multivariable			
	OR	95% CI		*P*	OR	95% CI		*P*
Male sex	1.42	1.12	1.79	.004	1.42	1.05	1.93	.022
Age group				<.001				.154
<1 yr	6.35	4.23	9.54	<.001	1.35	.74	2.43	.328
1 to <10 yr	Ref				Ref			
10-14 yr	1.87	1.42	2.47	<.001	1.39	.97	1.99	.071
Race				.550				.456
White	Ref				Ref			
Nonwhite	.86	.65	1.13	.275	.79	.54	1.15	.217
Missing	.97	.70	1.34	.855	.88	.54	1.43	.603
Initial WBC count $\times 10^9$/L				<.001				.015
<50,000	Ref				Ref			
≥50,000	2.89	2.20	3.78	<.001	1.58	1.09	2.28	.016
Missing	1.95	1.46	2.60	<.001	.79	.47	1.34	.385
Immunophenotype				<.001				<.001
B-precursor	Ref				Ref			
Mixed phenotype	17.52	9.50	32.34	<.001	34.32	16.64	70.79	<.001
T cell	2.12	1.47	3.04	<.001	1.77	1.07	2.91	.025
Missing	1.55	1.18	2.03	.002	1.24	.81	1.90	.333
Cytogenetics*				<.001				<.001
Favorable	.25	.17	.38	<.001	.44	.27	.72	.001
Standard	Ref				Ref			
Unfavorable	2.70	2.00	3.64	<.001	3.96	2.56	6.12	<.001
Diagnostic period				<.001				.013
2001-2005	Ref				Ref			
2006-2009	.73	.54	.98	.362	.81	.54	1.20	.285
2010-2013	.72	.54	.97	.361	.90	.59	1.38	.624
2014-2018	.36	.25	.52	<.001	.44	.26	.74	.002
Relapse before HSCT	30.85	23.51	40.48	<.001	32.77	23.89	44.96	<.001
Region†				.130				.165
West	.80	.61	1.06	.120	.60	.36	1.02	.058
Central	Ref				Ref			
East	.78	.59	1.03	.083	.70	.42	1.17	.174
Diagnosis at HSCT center	1.15	.91	1.46	.241	1.51	1.09	2.09	.013
Distance from treating center				.001				.025
0 to <100 km	Ref				Ref			
100 to <200 km	.79	.53	1.18	.246	.79	.47	1.32	.370
200 to <300 km	.67	.36	1.25	.207	.76	.35	1.65	.481
≥300 km	1.77	1.26	2.48	.001	1.84	1.17	2.91	.009
Neighborhood income quintile				.093				.436
1 (lowest)	Ref				Ref			
2	.73	.51	1.06	.096	.97	.61	1.55	.895
3	.81	.57	1.16	.250	.87	.55	1.37	.540
4	.64	.44	.93	.018	.79	.49	1.28	.345
5 (highest)	.98	.69	1.37	.886	1.27	.81	1.97	.301
Missing	1.38	.57	3.36	.482	.74	.13	4.11	.728

* Cytogenetic category defined as favorable (double trisomies of chromosome 4 and 10, t(12;21)), unfavorable (MLL rearrangement, t(9;22) Philadelphia chromosome, iAMP21, near haploidy/hypodiploid), and standard (all others).

† Region defined as West (British Columbia, Alberta, Saskatchewan, and Manitoba), Central (Ontario), and East (Quebec and Atlantic Provinces).

(OR, 1.77; 95% CI, 1.07 to 2.91; $P = .025$), unfavorable relative to standard cytogenetics (OR, 3.96; 95% CI, 2.56 to 6.12; $P < .0001$), relapse before HSCT (OR, 32.77; 95% CI, 23.89 to 44.96; $P < .0001$), diagnosis at an HSCT treating center (OR, 1.51; 95% CI, 1.09 to 2.09; $P = .013$), and living ≥ 300 km from the treating ALL center relative to living < 100 km away (OR, 1.84; 95% CI, 1.17 to 2.91; $P = .009$). Factors associated with lower odds of HSCT were favorable relative to standard cytogenetics (OR, .44; 95% CI, .27 to .72; $P = .001$) and recent diagnostic period (2014 to 2018) relative to most distant diagnostic period (2001 to 2005; OR, .44; 95% CI, .26 to .74; $P = .002$) (Table 2).

DISCUSSION

In this study using population-based data in the context of universal health insurance, we found that receipt of HSCT is significantly associated with poor prognostic indicators in pediatric ALL, including male sex, age group ≥ 10 years, initial WBC count ≥ 50,000 $\times 10^9$/L, T cell or MPAL immunophenotype, unfavorable

cytogenetics, and relapsed disease. The proportion of HSCT performed before first relapse (41.5%) was similar to that reported in a large Center for International Blood and Marrow Transplant Research (CIBMTR) registry analysis of pediatric patients from the United States between 2008 and 2014 [19]. However, we also found that those diagnosed with ALL at a center that also performs HSCT and those who lived the farthest away from their treating center were more likely to receive HSCT. Importantly, we also did not find an association between neighborhood income quintile or race and receipt of HSCT in pediatric ALL.

Patients who were initially diagnosed at an HSCT treatment center versus a non-HSCT center had a 1.5 times increased odds of receiving HSCT at some point during their ALL treatment. HSCT is provided at 6 (of 17) medium to large pediatric referral centers in major cities across Canada. Having upfront ALL treatment at an HSCT center may be advantageous in that patients and referring physicians have immediate access to HSCT physicians when discussing and debating therapy options that may include HSCT. In some centers, HSCT physicians may treat primary ALL patients, and most centers will have regular rounds with both leukemia and HSCT physicians present. Decision-making may be positively biased in favor of HSCT at centers that can offer this service. We did not find any difference in time to HSCT either from date of diagnosis (for patients receiving HSCT before a first relapse) or date of relapse (for patients receiving HSCT after first relapse), which suggests that referrals and HSCT assessments occur with equal speed when patients meet an indication for HSCT. However, it is also possible that families are more likely to decline HSCT if it means moving to another center to undergo the procedure, particularly in situations where the indication and outcome for HSCT is less certain.

Very little has been published regarding access to transplant services among children, and much of the literature comes from adults. Studies in the United States have shown disparities related to increasing age and gender, with women less likely to undergo HSCT [6,7]. Given the high cost of HSCT, patients with private medical insurance were more likely to receive HSCT than those with government issued coverage [2]. In the United States federal legislation to improve access to health insurance is anticipated to have a direct positive effect on access to HSCT [20]. Race, a common surrogate for socioeconomic status and health literacy, has been an inconsistent factor, with some studies showing differential access to HSCT [2,7] and others showing no differential access [6]. Only a few studies have examined differential access to HSCT in children [5–7]. Among patients younger than 18 years, 1 analysis from the CIBMTR found higher access among male patients with an OR of 1.3 (95% CI, 1.18 to 1.44), a finding similar to our study [5].

To our knowledge this is the first study to show that patients who live the farthest from their treatment centers were more likely to receive HSCT, a finding that challenges the belief that geographic distance is a barrier to specialized healthcare treatments. We found no difference in receipt of HSCT by relapse status across the distance categories, indicating that relapse status alone did not explain the higher rate of HSCT among those most distant from their treatment center. However, this finding should be considered hypothesis generating because the magnitude of effect is small and needs confirmation in future studies. Nonetheless, this finding may reflect the individual preferences of referring and HSCT physicians to provide a shorter duration, more definitive, consolidative therapy to these rural and remote patients. In cases where chemotherapy and HSCT are considered equivocal options, clinicians may factor distance into their decision-making. Alternatively, patients living in close proximity to their treatment centers may be preferentially offered investigational therapies in a clinical trial instead of HSCT.

Three previous studies have examined the effect of distance to the treating center and receipt of HSCT. The first study among elderly patients with advanced myelodysplastic syndrome reported no difference, whereas a second study among adults with leukemia and lymphoma showed that increasing distance to the treating center decreased the likelihood of receiving HSCT [21,22]. Among children with ALL, a pooled analysis of CIBMTR and Surveillance, Epidemiology, and End Results data in the United States showed no effect on place of residence and access to HSCT [23].

Other sociodemographic factors did not influence the receipt of HSCT in our population-based analysis, including race, geographic region, and census-derived neighborhood income. HSCT is a very costly procedure, and in countries with privatized healthcare disparities have been described by race and lower socioeconomic status [2]. A large study linking the Surveillance, Epidemiology, and End Results cancer registry and the CIBMTR registry showed that African Americans had lower rates of both autologous and allogeneic HSCT for treatment of leukemia, lymphoma, and multiple myeloma, suggesting that differences cannot be entirely explained by lack of donor availability [7]. However, among children younger than 20 years there was no difference in receipt of HSCT by race, which is consistent with our findings. Another study using hospital inpatient records at M. D. Anderson Cancer Center examined a pediatric subgroup under 18 years of age and similarly found no difference in access to HSCT and race [6]. Neither of these studies controlled for socioeconomic status. The lack of an association between race and neighborhood income quintile with receipt of HSCT in our study builds on these prior studies and further supports that such disparities do not exist for children in either the United States or Canada, regardless of health insurance status.

With the emergence of innovative targeted agents and chimeric antigen receptor T cells, HSCT practices are expected to change over time. In our recent study period (2014 to 2018), rates of HSCT appear to be lower than previous years, which is most likely due to a lack of mature follow-up data. However, these lower rates also may have been influenced by patients receiving innovative targeted therapies. Because these therapies are not well captured in the current version of CYP-C, we were unable to determine how this practice influenced receipt of HSCT. However, CYP-C will be modified in the near future to capture these elements, thus making this analysis feasible at a later time point.

In this study we show that HSCT access in pediatric ALL is largely influenced by strong, well-known, biologically driven, disease-related factors such as sex, age group, initial WBC, immunophenotype, cytogenetics, and relapsed status. Within Canada's vast geography, equitable access to HSCT was not limited by distance; in fact, patients farthest away from their treatment centers were more likely to receive HSCT, suggesting that geographic barriers are overcome with increased social support and provision of local housing, where possible. Within the Canadian healthcare system, universal access to high-cost services such as HSCT means that race and income are not relevant when considering such procedures.

The strengths of this study include a large population-based registry with representation from every pediatric cancer center in the country. This is the largest population-based cohort of children with ALL in which access to HSCT has been examined. The data are rich with detailed collection of disease-related and socioeconomic-demographic factors. Patients are included from the time of diagnosis and followed for 5 years, which allowed us to

describe the use of HSCT in relation to initial diagnosis and subsequent relapse. There is less HSCT use in the most recent diagnostic period because patients have not had enough follow-up time to relapse and require HSCT. However, these results should be interpreted in light of study limitations. The major limitation is the lack of data on donor availability, which would inform why patients did and did not undergo HSCT. In Canada our unique First Nations, Aboriginal, and Inuit patients make identifying unrelated donors a particular challenge for this population. In addition, patients over 15 years of age are not captured in the registry, and thus these results may not be generalizable to adolescents and young adults. Similar to other registry studies, we were unable to capture patient and physician preferences, which likely influence the final decision for HSCT. Further, missing race data made it difficult to conclude what role race may have played in access to HSCT. Finally, we did not evaluate outcomes of HSCT in relation to the examined factors; this examination will be the subject of future research using CYP-C data.

In conclusion, in our population-based analysis within a publically funded healthcare system, we found that children with ALL have equitable access to HSCT, which was largely influence by well-known, biologically driven prognostic factors. Importantly, socioeconomic factors such as income and race did not have any effect on receipt of HSCT. Although patients diagnosed at a center that also performs HSCT and those who live $\geq$ 300 km from their treating center were more likely to receive HSCT, the effect size was small, and future research should focus on understanding patient and provider preferences, referral and decision-making processes, and how these factors contribute to HSCT access.

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