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TRANSPLANTATION: RESEARCH ARTICLE

Regional differences in access to hematopoietic stem cell transplantation among pediatric patients with acute myeloid leukemia

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Abstract

Introduction: Indications for hematopoietic stem cell transplantation (HSCT) in pediatric acute myeloid leukemia (AML) are primarily dependent on risk stratification at diagnosis and relapse status. We sought to determine whether access to HSCT is influenced by regional and socioeconomic factors.

Methods: Children with newly diagnosed AML aged < 15 years between 2001 and 2015 were identified using the Cancer in Young People in Canada national population–based registry. Factors potentially associated with the receipt of HSCT were studied using univariate and multivariable logistic regression models.

Results: Overall, 568 children with newly diagnosed AML were included and 262 (46%) received HSCT. A greater proportion of patients, 103/157 (65.6%), underwent HSCT after first or subsequent relapse compared to 159/411 (38.7%) patients who underwent transplant before relapse. Among patients for whom HSCT would be considered before relapse, factors associated with higher odds of HSCT in a multivariable analysis were: poor versus good-risk cytogenetics (Odds ratio [OR]: 30.0, 95% confidence interval [CI]: 7.7–117.0), diagnosis during 2012–2015 versus 2001–2006 (OR: 3.2, 95% CI: 1.6–6.3), diagnosis in eastern Canada versus central Canada (OR: 3.7, 95% CI: 1.9–7.3), and age 10–14 years versus age < 1 year (OR: 5.4, 95% CI: 2.3–12.8). Among patients for whom HSCT would be considered after first relapse, higher odds of HSCT was associated with diagnosis at a HSCT center (OR: 2.1, 95% CI: 1.1–4.1).

Conclusion: Patients diagnosed at a HSCT performing center and patients from eastern Canada had higher odds of receiving HSCT. This may suggest preferential access to HSCT for certain patients.

KEYWORDS

access to care, acute myeloid leukemia, geographical, hematopoietic stem cell transplant, sociodemographic, universal health care

1 | INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a common treatment for children with acute myeloid leukemia (AML). In contrast to systemic cancer therapy, the provision of HSCT is more geographically restrictive and only offered at certain specialized centers due to the

Abbreviations: AML, acute myeloid leukemia; CIBMTR, Centre for International Bone Marrow Transplant Registry; COG, Children's Oncology Group; CR1, First complete remission; CYP-C, Cancer in Young People in Canada; FAB, French-American-British; HSCT, Hematopoietic stem cell transplantation; MRD, Minimal residual disease; POGO, Pediatric Oncology Group of Ontario; POGONIS, Pediatric Oncology Group of Ontario Networked Information System.

need for more intense resources, the availability of expertise across multiple subspecialties, and the high cost of this procedure.[1] As such, equitable access to HSCT is a worldwide issue and disparities have been reported even within high-income regions, including North America, the United Kingdom, and Europe.[2–4]

In pediatric AML, risk stratification incorporating cytogenetics features and remission status, including minimal residual disease (MRD), is used to identify children who can be treated with chemotherapy alone, reserving HSCT for those with high-risk disease at presentation or relapsed disease.[5,6] However, indications for HSCT in first complete remission (CR1) continue to evolve, especially as systemic therapy has changed over time.[7] In addition to established indications published by both the American Society for Blood and Marrow Transplantation and the European Society for Blood and Marrow Transplantation for HSCT in pediatric AML, HSCT practices are also guided by recommendations within clinical trials.[8,9]

Disparities in access to HSCT have been reported by age,[10] gender,[11,12] race,[12,13] and insurance status.[2,14] Regional and geographical variations in access to HSCT have been well described in multiple diseases, including leukemia and Hodgkin lymphoma in both the allogeneic and autologous settings.[15,16]

Very few studies have examined access to HSCT among children and usually have included children as a subgroup analysis from larger adult studies.[10–12] These studies lack data on risk factors that may influence the decision to proceed to HSCT at the time of initial diagnosis. Furthermore, few studies have examined access to HSCT within a publically funded health care system. Recently, we reported geographical variability in access to HSCT in Canadian children with acute lymphoblastic leukemia suggesting possible preferential referral patterns.[17]

The Cancer in Young People in Canada (CYP-C) program maintains a national childhood cancer surveillance and research registry that includes population-level data on all new malignant diagnoses treated at the 17 Canadian pediatric tertiary care centers since 2001. Canada has a national publically funded universal health care system but the provision of health services is administered by the individual provinces and territories. Referral for HSCT services is available across the country but is offered only at six specialized urban centers. We sought to determine whether sociodemographic and regional-geographic factors influence the receipt of HSCT in pediatric AML.

2 | METHODS

2.1 | Study population

Patients aged less than 15 years with newly diagnosed AML, treated at any of the 17 pediatric oncology centers in Canada were included. All AML subtypes (ICDO M codes 9840, 9861, 9867, 9871:9874, 9891, 9895–9897, 9898, 9910) with the exception of acute promyelocytic leukemia were included. We excluded those with a previous malignancy diagnosis or previous solid-organ transplantation or HSCT prior to AML. The study period included patients with new diagnoses between January 1, 2001 and December 17, 2015, but patients may have received HSCT at a later date.

2.2 | Registry data

CYP-C is a population-based registry that includes all children less than 15 years old diagnosed with cancer and treated at one of the 17 tertiary pediatric oncology centers in Canada. The federal Public Health Agency of Canada administers CYP-C in collaboration with the C17 Council and the Canadian Partnership against Cancer. All new pediatric cancers diagnosed since 2001 and outcomes for 5 years following diagnosis or an eligible second malignancy are captured. Data are abstracted locally and submitted to CYP-C in two ways. Within Ontario, data are transferred to CYP-C via the Pediatric Oncology Group of Ontario (POGO) Networked Information System (POGONIS), a provincial population-based registry that predates CYP-C. Outside of Ontario, the 12 remaining centers enter data directly into CYP-C. The proportion of cases captured by both POGO and CYP-C is 96%.[18,19] Common elements in both databases include: demographic variables including date of birth, sex, race, and postal code; diagnostic and treatment details; treatment plan details including HSCT; and outcomes such as relapse, second malignancy, and death.

The CYP-C program ensures high-quality data through several mechanisms. Each site's data manager belongs to a community of practice that engages in monthly review teleconferences and an annual face-to-face training meeting combined with periodic site audits and data validation checks.

2.3 | Outcomes and predictors of interest

The primary outcome of interest was receipt of first HSCT. Factors potentially associated with HSCT were examined as follows: (a) Demographic features: age at AML diagnosis (< 1 year, 1 to < 10 years, and 10–14 years), sex, race (White vs non-White), diagnostic period (2001–2006, 2007–2011, and 2012–2015); (b) leukemia features: AML French-American-British (FAB) subtype, cytogenetic classification (good, intermediate, poor); (c) treatment center features: region (west, central, and east), if treatment center also provides HSCT; and (d) geographic/socioeconomic features: distance to treatment center (in kilometers [km]) and neighborhood-level income quintile. Cytogenetic groups were based on Children's Oncology Group (COG) AAML0531 risk classification defined as: good—the presence of t(8;21) or t(16;16)/inv(16) regardless of monosomy 7, monosomy 5, or del5q; poor—the presence of monosomy 7, monosomy 5, or del5q without t(8;21) or t(16;16)/inv(16) and FLT3/ITD regardless of good cytogenetic features; and intermediate including all others.[5,20] The region of AML treatment center was categorized as follows: West—British Columbia, Alberta, Saskatchewan, and Manitoba; Central—Ontario; and East—Quebec and the Atlantic provinces. In Canada, 6 of the 17 pediatric cancer centers also provide HSCT; we examined whether the treating center was also an HSCT center. Residential postal codes at the time of diagnosis were used to determine distance to the treatment center, calculated as a straight line from the geographic center of the

postal code area, and stratified into 100-km increments with the last category being ≥ 300 km. Postal codes were also used to determine neighborhood-level socioeconomic status. Full six-digit postal codes were available for all provinces except for British Columbia in which three-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.[21–23]

2.4 | Statistical plan

In AML, HSCT is used in two distinct settings, namely in first remission for those with high-risk disease and following relapse as salvage therapy. As these two populations are different, we made a pragmatic decision to separate the cohort into two groups for a stratified analysis. In Group 1, we included patients for whom HSCT would be considered before relapse defined as those who did not relapse prior to HSCT or never relapsed. Among this group, we compared those who received HSCT with those who did not. In Group 2, we included patients for whom HSCT would be considered after the first relapse, defined as those with relapse prior to HSCT or relapse without HSCT, comparing those who received HSCT with those who did not. We evaluated the variables associated with receiving HSCT using univariate and multivariable logistic regression models and associations were estimated using odds ratios (OR) with 95% confidence intervals (CI). In the first group (relapse-naïve patients), because of the large number of events (HSCTs), all considered predictors were included in a multivariable analysis. However, in the second group, given the small number of patients who did not receive HSCT, we could not reliably perform a multivariable analysis and thus only a univariate analysis is shown. As mandated by the CYP-C program in order to protect patient privacy, cell sizes less than 5 were suppressed and reported as <5, where indicated.

We also compared time to HSCT from diagnosis or relapse between those diagnosed at an HSCT center versus a non-HSCT center using the Wilcoxon rank sum test. Statistical significance was defined as P value < 0.05. Statistical analysis was conducted using the SAS statistical program (SAS-PC, version 9.4; SAS Institute Inc, Cary, North Carolina).

3 | RESULTS

Among 583 patients with AML, 15 patients were excluded who had a prior malignancy or a prior solid-organ transplant. The remaining 568 patients made up the study cohort, with 262 patients (46%) receiving HSCT. Features of the overall cohort are shown in Table 1 and displayed separately for those who did not relapse prior to HSCT or never relapsed (Group 1) compared to those with relapse prior to first HSCT or those who relapsed without any HSCT (Group 2).

Of the 262 patients who received HSCT, 159 (60.7%) underwent transplant before relapse (Group 1), 94 (35.9%) underwent first HSCT after first relapse and 9 (3.4%) underwent first HSCT after second relapse (Group 2, n = 103). HSCT-naïve relapses (relapses without a prior HSCT) are shown following first and second relapse and were treated with HSCT in 94/103 (91.3%) and 9/9 (100%) patients, respectively (Figure 1). Of note, there were no HSCT-naïve relapses that occurred after third or subsequent relapse.

3.1 | Group 1: Patients for whom HSCT would be considered before relapse

Among the first group, in univariate analysis, factors significantly associated with receipt of HSCT prior to first relapse included age at diagnosis, AML FAB subtype, cytogenetics, diagnostic period, and geographic region of treatment center (Table 2). Among patients for whom HSCT would be considered before relapse, factors associated with higher odds of HSCT in a multivariable analysis were poor and intermediate-risk relative to good-risk cytogenetics (OR: 30.0, 95% CI: 7.7–117.0 and OR 11.9, 95% CI 3.9–36.1), diagnostic period in 2007–2011 and 2012–2015 relative to 2001–2006 (OR: 2.7, 95% CI: 1.5–4.9, and OR: 3.2, 95% CI: 1.6–6.3), being diagnosed in eastern Canada relative to central Canada (OR: 3.7, 95% CI: 1.9–7.3), and age 1 to < 10 years and age 10–14 years relative to age < 1 year (OR: 4.3, 95% CI: 2.1–9.1 and OR: 5.4, 95% CI: 2.3–12.8) (Table 2). No association was found between sex, race, distance from treatment center, initial diagnosis at an HSCT performing center, and neighborhood-level income with receipt of HSCT.

3.2 | Group 2: Patients for whom HSCT would be considered after first relapse

In univariate analysis among the second group, the only factor significantly associated with receipt of HSCT after first relapse was diagnosis at an HSCT performing center (OR: 2.1, 95% CI: 1.1–4.1) (Table 3).

3.2.1 | Time to HSCT from diagnosis and relapse

For patients who received HSCT before relapse, there was no difference in length of time from AML diagnosis to receipt of HSCT among those diagnosed at an HSCT center versus a non-HSCT center (median 135 days, IQR [interquartile range] 108–156 days vs. 130 days [IQR 111–170 days], respectively, P = 0.86). For patients who received HSCT after first relapse, there was a significantly shorter difference in time from relapse date to HSCT for those diagnosed at an HSCT center versus at a non-HSCT center (median 89 days [IQR 77 to 113] vs median 100 days [IQR 84 to 137], respectively, P = 0.017).

3.2.2 | Donor source

In a posthoc analysis, in order to further explore the association between geographical region with HSCT prior to relapse, the relationship between donor source and region was evaluated. Patients diagnosed in eastern Canada and receiving HSCT had a higher

TABLE 1 Characteristics of the study population stratified by relapse status at HSCT

	Group 1: Patients for whom HSCT would be considered before relapse (did not relapse prior to HSCT or never relapsed)				Group 2: Patients for whom HSCT would be considered after first relapse (relapse prior to HSCT or relapse without HSCT)			
	Overall cohort		Received HSCT		Overall cohort		Received HSCT	
	N = 411		N = 159		N = 157		N = 103	
Characteristics	n	%	n	%	n	%	n	%
Sex								
Female	211	51.3	88	55.3	74	47.1	46	44.7
Male	200	48.7	71	44.7	83	52.9	57	55.3
Age at diagnosis								
<1 year	80	19.5	14	8.8	21	13.4	10	9.7
1 to <10 years	233	56.7	103	64.8	88	56.1	62	60.2
10–14 years	98	23.8	42	26.4	48	30.6	31	30.1
Race								
White	235	57.2	94	59.1	93	59.2	61	59.2
Non-White	117	28.5	45	28.3	43	27.4	30	29.1
Not available	59	14.4	20	12.6	21	13.4	12	11.7
AML FAB subtype								
AML-M0	28	6.8	16	10.1	13	8.3	8	7.8
AML-M1	29	7.1	16	10.1	10	6.4	10	9.7
AML-M2	79	19.2	27	17.0	24	15.3	19	18.4
AML-M4/M4Eo	48	11.7	13	8.2	27	17.2	18	17.5
AML-M5/M6	67	16.3	30	18.9	41	26.1	23	22.3
AML-M7	51	12.4	18	11.3	15	9.6	10	9.7
AML-NOS	59	14.4	32	20.1	12	7.6	6	5.8
AML-other[a]	50	12.2	7	4.4	15	9.6	9	8.7
Cytogenetics[b]								
Good	60	14.6	<5	2.5	21	13.4	14	13.6
Intermediate	315	76.6	128	80.5	133	84.7	87	84.5
Poor	36	8.8	27	17.0	<5	1.9	<5	1.9
Diagnostic period								
2001–2006	150	36.5	44	27.7	48	30.6	32	31.1
2007–2011	131	31.9	56	35.2	64	40.8	46	44.7
2012–2015	130	31.6	59	37.1	45	28.7	25	24.3
Region of treating center[c]								
West	131	32.1	44	27.8	45	28.8	28	27.5
Central	163	40.0	50	31.6	76	48.7	52	51.0
East	114	27.9	64	40.5	35	22.4	22	21.6
Diagnosis at HSCT center								
Yes	275	66.9	111	69.8	99	63.1	71	68.9
No	136	33.1	48	30.2	58	36.9	32	31.1
Distance from treating center[d]								
0 to <100 km	289	71.7	114	73.1	119	77.3	77	76.2
100 to <200 km	41	10.2	14	9.0	14	9.1	12	11.9
200 to <300 km	26	6.5	6	3.8	9	5.8	<5	4.0
≥ 300 km	47	11.7	22	14.1	12	7.8	8	7.9

(Continues)

TABLE 1 (Continued)

Characteristics	Group 1: Patients for whom HSCT would be considered before relapse (did not relapse prior to HSCT or never relapsed)				Group 2: Patients for whom HSCT would be considered after first relapse (relapse prior to HSCT or relapse without HSCT)			
	Overall cohort		Received HSCT		Overall cohort		Received HSCT	
	N = 411		N = 159		N = 157		N = 103	
	n	%	n	%	n	%	n	%
Neighborhood income quintile								
1 (lowest)	71	17.3	28	17.6	33	21.0	24	23.3
2	80	19.5	28	17.6	35	22.3	19	18.4
3	81	19.7	33	20.8	29	18.5	16	15.5
4	80	19.5	24	15.1	36	22.9	27	26.2
5 (highest)	94	22.9	45	28.3	22	14.0	17	16.5
Missing	5	1.2	<5	0.6	<5	1.3	0	0.0

Abbreviations: AML, acute myeloid leukemia; FAB, French American British; HSCT, hematopoietic stem cell transplantation; NOS, not otherwise specified

[a] AML-other includes 27 patients with AML in Down syndrome with < 5 receiving HSCT.

[b] Cytogenetic category defined as: good—the presence of t(8;21) or t(16;16)/inv(16) regardless of monosomy 7, monosomy 5, or del5q; poor—the presence of monosomy 7, monosomy 5, or del5q without t(8;21) or t(16;16)/inv(16) and FLT3/ITD; and intermediate including all others.

[c] Region defined as: West—British Columbia, Alberta, Saskatchewan, and Manitoba; Central—Ontario; and East—Quebec and Atlantic Provinces (missing n = 4).

[d] Distance from treatment center (missing n = 8).

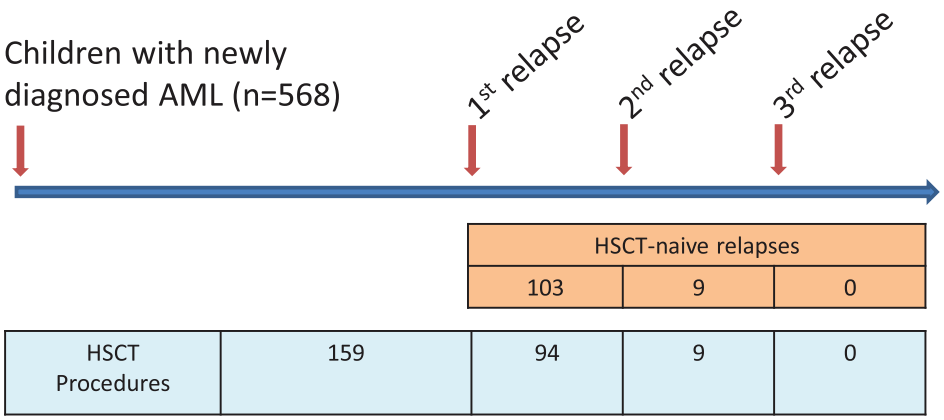

FIGURE 1 Timing of hematopoietic stem cell transplantation relative to relapse. HSCT-naïve relapses represent the number of relapses that occurred without a prior HSCT. Abbreviations: AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplant

proportion of matched related donors compared to patients from western and central Canada (43% vs 31.9% vs 22.6%, respectively, $P = 0.0007$) (Table 4). This availability of matched related donors was only seen in patients who received HSCT before relapse ($P = 0.003$) and not for patients who received HSCT after first relapse as part of salvage treatment ($P = 0.26$).

3.2.3 | Impact of clinical trial and registration status

The majority of patients were treated according to the frontline COG studies (32.4% of patients on AAML0531, 19.4% of patients on AAML1031, and 6.5% of patients on AAML03P1), followed by UKMRC10 (6.1%), and POG9421 (5.7%), as both registered and non-registered patients. No particular treatment protocol was associated with an increased rate of HSCT. Overall, 147 (26.3% of 560 patients) patients were registered and enrolled on an active clinical trial. Of those registered on a clinical trial, 66/147 (44.9%) received HSCT compared to 196/217 (47.4%) of nonregistered patients ($P = 0.59$).

4 | DISCUSSION

In this study, almost half of all children with AML received HSCT during their treatment. The majority of these children (60.7%) received HSCT prior to any relapse. Among patients for whom HSCT would be considered before relapse (Group 1), we found higher odds of receiving HSCT among patients with poor risk cytogenetics, age older than 1 year, diagnosed during the most recent two diagnostic periods (2007–2011 and 2012–2015 relative to 2001–2006), and being diagnosed in eastern Canada. The only factor significantly associated with the receipt of HSCT after first relapse was diagnosis at an HSCT performing center. Recent data published by the Centre for International Bone Marrow

TABLE 2 Factors associated with HSCT in patients for whom HSCT would be considered before relapse (Group 1: did not relapse prior to HSCT or never relapsed)

	Univariate				Multivariable			
Variable	**Odds ratio**	**95% CI**		***P* value**	**Odds ratio**	**95% CI**		***P* value**
Male sex	0.8	0.5	1.1	0.20	0.9	0.6	1.5	0.703
Age group				**0.0002**				**0.0002**
<1 year	Ref				Ref			
1 to <10 years	3.7	2.0	7.0	<0.0001	4.3	2.1	9.1	0.0001
10–14 years	3.5	1.8	7.1	0.0004	5.4	2.3	12.8	0.0002
Race				0.69				0.984
White	Ref				Ref			
Non-White	0.9	0.6	1.5	0.781	1.0	0.5	1.8	0.966
Missing	0.8	0.4	1.4	0.391	0.9	0.4	2.2	0.856
AML FAB subtype				**0.0002**				**0.057**
AML-M0	8.2	2.7	24.5	0.0002	7.9	2.0	31.2	0.003
AML-M1	7.6	2.6	22.3	0.0003	5.1	1.4	18.7	0.014
AML-M2	3.2	1.3	8.0	0.0139	3.2	1.0	10.1	0.052
AML-M4/M4Eo	2.3	0.8	6.3	0.1136	3.0	0.8	10.6	0.095
AML-M5/M6	5.0	2.0	12.7	0.0007	3.9	1.3	11.9	0.019
AML-M7	3.4	1.3	9.0	0.016	2.1	0.6	6.9	0.246
AML-NOS	7.3	2.8	18.8	<0.0001	4.8	1.5	15.3	0.008
AML-other[a]	Ref				Ref			
Cytogenetics[b]				**< 0.0001**				**< 0.0001**
Good	Ref				Ref			
Intermediate	9.6	3.4	27.1	<0.0001	11.9	3.9	36.1	<0.0001
Poor	42.0	11.9	148.7	<0.0001	30.0	7.7	117.0	<0.0001
Diagnostic period				**0.012**				**0.001**
2001–2006	Ref				Ref			
2007–2011	1.8	1.1	3.0	0.268	2.7	1.5	4.9	0.002
2012–2015	2.0	1.2	3.3	0.064	3.2	1.6	6.3	0.001
Region[c]				**<0.0001**				**<0.0001**
West	1.1	0.7	1.9	0.595	1.1	0.5	2.1	0.868
Central	Ref				Ref			
East	2.9	1.8	4.8	<0.0001	3.7	1.9	7.3	0.0002
Diagnosis at HSCT center	1.2	0.8	1.9	0.321	1.4	0.8	2.5	0.208
Distance from Treating center[d]				0.234				0.154
0 to < 100 km	Ref				Ref			
100 to < 200 km	0.8	0.4	1.6	0.515	0.8	0.4	2.0	0.682
200 to < 300 km	0.5	0.2	1.2	0.107	0.3	0.1	1.0	0.048
≥ 300 km	1.4	0.7	2.5	0.341	1.5	0.7	3.3	0.349
Neighborhood income quintile				0.17				0.444
1 (lowest)	Ref				Ref			
2	0.8	0.4	1.6	0.573	0.9	0.4	2.0	0.755

(Continues)

TABLE 2 (Continued)

	Univariate				Multivariable			
Variable	Odds ratio	95% CI		*P* value	Odds ratio	95% CI		*P* value
3	1.1	0.6	2.0	0.870	0.8	0.4	1.9	0.647
4	0.7	0.3	1.3	0.224	0.7	0.3	1.5	0.301
5 (highest)	1.4	0.8	2.6	0.281	1.3	0.6	2.9	0.459

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; FAB, French American British; HSCT, hematopoietic stem cell transplantation; NOS, not otherwise specified

[a] AML-other includes 24 patients with AML in Down syndrome with < 5 receiving HSCT.

[b] Cytogenetic category defined as: good—the presence of t(8;21) or t(16;16)/inv(16) regardless of monosomy 7, monosomy 5, or del5q; poor—the presence of monosomy 7, monosomy 5, or del5q without t(8;21) or t(16;16)/inv(16) and FLT3/ITD; and intermediate including all others.

[c] Region defined as: West—British Columbia, Alberta, Saskatchewan, and Manitoba; Central—Ontario; and East—Quebec and Atlantic Provinces (missing n = 3).

[d] Distance from treatment center (missing n = 8).

Bold font indicates statistical significance.

Transplant Registry (CIBMTR) among pediatric AML patients showed that transplant rates in CR1 (52%) plus primary induction failure (5–10%) was similar to the 61% of HSCT that occurred prior to relapse, as observed in our cohort.[24]

Age is not typically used for risk stratification in pediatric AML, but studies from both North America and the United Kingdom have demonstrated inferior survival for children over 10 years of age.[5,6,25] Older children had higher odds of receiving HSCT in our cohort likely indicating a higher prevalence of poor-risk features such as t(6;9) and FLT3-ITD status in children over 10 years.[26,27] A higher rate of HSCT in recent years was noted for the group of children in whom HSCT would be considered prior to relapse (Group 1), indicating that more recent risk stratification may have led to more patients being treated with HSCT, especially with the increasing availability of MRD testing. In addition, FLT3-ITD with high allelic ratio was recognized as a poor risk factor[27,28] and routine testing for this mutation occurred only in the recent two diagnostic periods.

Interestingly, we found that patients who were diagnosed in eastern Canada (including Quebec and the Atlantic provinces) had higher odds of receiving HSCT compared to central and western Canada. This finding may suggest a possible referral bias in eastern Canada as there was no difference between western and central Canada. However, indications for HSCT in children are not known to vary across Canada and centers generally follow uniform collaborative group recommendations. When donor source was reviewed, we found that eastern patients who received HSCT were more likely to have a matched related donor (sibling, parent or other related), compared to central and western Canada, suggesting that regional differences may be related to donor availability, in particular family size.

In Canada, HSCT is only offered at 6 of the 17 pediatric cancer centers across the country. Eligible patients are referred to their nearest transplant center and must relocate for the period of treatment and follow-up. In our cohort, among patients for whom HSCT would be considered after relapse (Group 2), those who had their initial diagnosis made at a center that also performs HSCT had twice the odds of receiving HSCT. Similarly, an adult study of lymphoma patients in Nebraska showed that use of HSCT among patients seen at university-based centers was significantly higher compared with community-based centers.[29] In our most recent study on children with acute lymphoblastic leukemia, initial diagnosis at an HSCT performing center led to 1.5 times odds of receiving HSCT.[17] We hypothesized that the ease of referral for HSCT in these larger centers contributed to higher rates of HSCT. In addition, the lack of geographical barriers/distance, since these patients would not need to relocate to another center for HSCT, may also have contributed to this finding. This hypothesis is supported by the significantly shorter time from relapse to HSCT for those who were diagnosed at an HSCT center versus a non-HSCT center in the postrelapse setting, suggesting that logistical issues (ease of referrals, lack of patient relocation) at such centers facilitate timely access to HSCT.

In children, only a few studies have examined factors that influence access to HSCT.[10–12] In a large analysis from the CIBMTR, male patients with acute lymphoblastic leukemia had 1.3 times of the odds of receiving HSCT, but the odds were not different following relapse.[11] Studies of race, generally a surrogate for socioeconomic status, have shown poorer access to HSCT among adult minorities including African Americans and Hispanics.[2,12,13] However, among children, the impact of race has not been demonstrated in several studies,[10,12] which may in part be due to uniform referral practices and wider availability of health care coverage. Among our cohort, we did not find any association between sex, race, distance from treatment center, and neighborhood-level income with the receipt of HSCT. The accessibility and use of cord blood units, especially in children where cell dose per kilogram of recipient weight is usually not preclusive, may allow the option of more donors, thereby annulling any effect of race in children compared to adults. Though the recommendations for HSCT in first remission have changed over time from one study to the next, we found no effect of treatment protocol or registration on a clinical trial with rates of HSCT.

Both Canada and the United States are geographically vast countries and disparities related to region have been reported. A pooled analysis of CIBMTR and SEER data in the United States showed lower transplant rates among adult AML patients from rural areas and areas of higher poverty, but no effect was seen in children.[30] Similarly, a smaller study from Manitoba, Canada found a nonsignificant trend showing that rural patients were less likely to receive autologous

TABLE 3 Factors associated with HSCT in patients for whom HSCT would be considered after first relapse (Group 2: relapse prior to HSCT or relapse without HSCT)

	Univariate			
Variable	**Odds ratio**	**95% CI**		***P* value**
Male sex	1.3	0.7	2.6	0.392
Age group				0.1489
<1 year	Ref			
1 to <10 years	2.6	1.0	6.9	0.05
10–14 years	2.0	0.7	5.7	0.19
Race				0.610
White	Ref			
Non-White	1.2	0.6	2.6	0.631
Missing	0.7	0.3	1.8	0.468
AML FAB Subtype[a]				0.368
AML-M0/1	2.4	0.6	10.0	0.231
AML-M2	2.5	0.6	10.6	0.202
AML-M4/M4Eo	1.3	0.4	4.9	0.666
AML-M5/M6	0.9	0.3	2.8	0.794
AML-M7	1.3	0.3	5.9	0.705
AML-NOS	0.7	0.1	3.1	0.604
AML-other[b]	Ref			
Cytogenetics[c]				0.993
Good	Ref			
Intermediate	1.0	0.4	2.5	0.91
Poor	1.0	0.1	13.0	1.0
Diagnostic period				0.211
2001–2006	Ref			
2007–2011	1.3	0.6	2.9	0.171
2012–2015	0.6	0.3	1.5	0.104
Region[d]				0.739
West	0.8	0.4	1.7	0.487
Central	Ref			
East	0.8	0.3	1.8	0.564
Diagnosis at HSCT center	2.1	1.1	4.1	**0.037**
Distance from Treating center[e]				0.267
0 to < 100 km	Ref			
100 to < 200 km	3.3	0.7	15.3	0.132
200 to < 300 km	0.4	0.1	1.7	0.235
≥ 300 km	1.1	0.3	3.8	0.892
Neighborhood income quintile				0.151
1 (lowest)	Ref			
2	0.5	0.2	1.2	0.118
3	0.5	0.2	1.3	0.153
4	1.1	0.4	3.3	0.830
5 (highest)	1.3	0.4	4.5	0.705

(Continues)

TABLE 3 (Continued)

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; FAB, French American British; HSCT, hematopoietic stem cell transplantation; NOS, not otherwise specified

[a] FAB subtype M0 and M1 combined due to small numbers.

[b] AML-other includes < 5 patients with AML in Down syndrome with < 5 receiving HSCT.

[c] Cytogenetic category defined as: good—the presence of t(8;21) or t(16;16)/inv(16) regardless of monosomy 7, monosomy 5, or del5q; poor—the presence of monosomy 7, monosomy 5, or del5q without t(8;21) or t(16;16)/inv(16) and FLT3/ITD; and intermediate including all others.

[d] Region defined as: West—British Columbia, Alberta, Saskatchewan, and Manitoba; Central—Ontario; and East—Quebec and Atlantic Provinces (missing n = 3).

[e] Distance from treatment center (missing n = 8).

HSCT for Hodgkin lymphoma compared to urban patients (31% vs 69% respectively).[16] Differences in the health care system between these two countries may partly explain these findings.

The strengths of this study include representation from every pediatric cancer center in the country within a large population-based registry. The Canadian health care system eliminates the bias of private insurance status which is an ideal setting to determine whether true "universal access" to health care services exists and if it is influenced by additional factors. The CYP-C program contains detailed information of disease-related and socioeconomic–demographic factors. Unlike other HSCT registries, patients are included from the time of initial diagnosis and followed for 5 years, which allowed us to describe the use of HSCT in relation to features present at the time of initial diagnosis and subsequent relapse.

Limitations include the retrospective nature of this study and lack of data regarding donor availability at the time of diagnosis, which would explain why some patients did or did not receive HSCT. A current limitation of CYP-C is that it does not include data on MRD results and methods, which may have informed decision making for HSCT. Distance was calculated using the geographic center point for postal code areas and therefore the actual distance between the patient's home and treatment center was approximated. Like other registry studies, we do not have information on specific referral rates/patterns and provider/patient preferences for proceeding to HSCT. Given the strong influence of relapse on receipt of HSCT, we stratified our population into those who would be considered for HSCT prior to relapse and those who would be considered for HSCT after first relapse. We appreciate this division is not perfect as in some patients, there would have been in an intent to perform HSCT but a donor may not have been identified, the patient may have had conditions that precluded HSCT, or the patient may have relapsed/progressed prior to receiving the planned HSCT. Nonetheless, this division was used to improve homogeneity of each group; all analyses were stratified by this variable. Finally, we did not evaluate differences in survival related to access to HSCT as that will be the focus of a future manuscript.

TABLE 4 HSCT donor type by region

Donor type	Matched related donor	Matched unrelated donor	Other (not specified/not available)	*P* value
Overall HSCT cohort (n = 260)				
Western Canada	23 (31.9%)	33 (45.83%)	16 (22.2%)	0.0007
Central Canada	23 (22.6%)	58 (56.9%)	21 (20.6%)	
Eastern Canada	37 (43.0%)	22 (25.6%)	27 (31.4%)	
Total	83 (31.9%)	113 (43.5%)	64 (24.6%)	
Patients who received HSCT before relapse (n = 158)[a]				
Western Canada	18 (40.9%)	17 (38.6%)	9 (20.5%)	0.002
Central Canada	9 (18.0%)	28 (56.0%)	13 (26.0%)	
Eastern Canada	31 (48.4%)	14 (21.9%)	19 (29.7%)	
Total	58 (36.7%)	59 (37.3%)	41 (26.0%)	
Patients received HSCT after relapse (n = 102)[b]				
Western Canada	5 (17.9%)	16 (57.1%)	7 (25.0%)	0.26
Central Canada	14 (26.9%)	30 (57.7%)	8 (15.38%)	
Eastern Canada	6 (27.3%)	8 (36.4%)	8 (36.4%)	
Total	25 (24.5%)	54 (52.9%)	23 (22.6%)	

Abbreviations: HSCT, hematopoietic stem cell transplantation.
[a] One region missing.
[b] One region missing.

5 | CONCLUSIONS

Pediatric AML patients had equitable access to HSCT within the Canadian publically funded health care system, with no differences seen by socioeconomic factors such as race, distance to treatment center, and income level. We found that patients from eastern Canada had higher odds of receiving HSCT. For patients with AML relapse, initial diagnosis at an HSCT performing center conferred a higher odds of receiving HSCT and a shorter time from relapse to receipt of HSCT. Future study and understanding of specific referral and decision-making processes, both among patients and providers, will add further clarity to regional and socioeconomic access to HSCT.

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CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available by application to the Canada in Young People in Canada program. The data are not publicly available due to privacy or ethical restrictions.

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