Enrolling children with acute lymphoblastic leukaemia on a clinical trial improves event-free survival: a population-based study

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Background: The objectives of this study were to describe the impact of trial enrollment at diagnosis on event-free and overall survival in paediatric acute lymphoblastic leukaemic (ALL) using a population-based approach.

Methods: We conducted a retrospective cohort study that included children newly diagnosed with ALL between 1 and 14 years of age. The data source was the Cancer in Young People in Canada (CYP-C) national paediatric cancer population-based database. We conducted univariate and multiple Cox proportional hazards models.

Results: There were 2569 children with ALL; 1408 (54.8%) were enrolled on a clinical trial at initial diagnosis. Event-free survival at 5 years was 89.8% ± 0.9 vs 84.1% ± 1.2. (P < 0.0001) for those enrolled and not enrolled on a clinical trial, respectively. Overall survival at 5 years was higher for those enrolled (94.1% ± 0.7) vs not enrolled (90.5% ± 1.0; P = 0.001). In a model that adjusted for demographic, leukaemic and socioeconomic factors, enrollment on trials was significantly associated with better event-free survival (hazard ratio (HR) 0.67, 95% confidence interval (CI) 0.47–0.95; P = 0.023), but not overall survival (HR 0.69, 95% CI 0.44–1.08; P = 0.102).

Conclusions: Event-free survival was significantly better in children with ALL enrolled on a clinical trial. Future research should identify barriers to clinical trial enrollment for children with ALL.

There has been debate about the impact of enrollment on clinical trials and survival outcomes for children with cancer. Retrospective studies found that patients enrolled on clinical trials have better outcomes compared with patients not enrolled on clinical trials (Stiller and Eatock, 1994; Wagner *et al*, 1995). However, a systematic review determined that these studies were limited because of confounding and selection bias, and thus concluded that the impact of trial enrollment is not clear (Peppercorn *et al*, 2004).

Further, a Cochrane review found that, in general, outcomes are similar between those who do and those who do not participate in randomised trials (Vist *et al*, 2008).

We recently used the Cancer in Young People in Canada (CYP-C) database, a national paediatric cancer population-based data source, to describe the proportion of all children with cancer enrolled on a clinical trial and to describe factors associated with enrollment. About one in four children with cancer were enrolled

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on a clinical trial (Pole *et al*, 2017). The most common reasons cited for non-enrollment were lack of an available trial and physician choice. Acute lymphoblastic leukaemic (ALL) is the most common paediatric cancer, accounting for approximately one-third of all cancers in children aged 0–14 years of age. We found that children with ALL had the highest rates of enrollment among paediatric cancer diagnoses (Pole *et al*, 2017).

Given this data, we next wanted to determine if enrollment on a clinical trial is associated with better survival for children with ALL. Therefore, the objectives of this analysis were to describe the impact of trial enrollment at diagnosis on event-free survival (EFS) and overall survival (OS) in paediatric ALL.

MATERIALS AND METHODS

Population of interest and sampling methods. We included children with newly diagnosed ALL with ICD-O M codes 9835, 9836 and 9837; these codes define patients with precursor lymphoblastic leukaemic NOS, B-cell and T-cell, respectively. Other inclusion criteria were 1–14 years of age, diagnosed between 01 January 2001 and 31 December 2012, and treated at one of the 17 paediatric oncology centres in Canada. We excluded patients in whom enrollment status was unknown, those diagnosed <1 year of age (infant ALL) and those with Burkitt's leukaemic. We chose to exclude infant and Burkitt's ALL as the treatment approach is fundamentally different compared with precursor lymphoblastic leukaemic.

Data source. We used the data from CYP-C, a population-based registry that aims to include all paediatric patients with cancer diagnosed between 0 and 14 years of age since 2001, who were diagnosed and treated at one of the 17 tertiary paediatric oncology centres in Canada. Two data collection approaches are used for CYP-C data. For the 5 centres in Ontario, the data are transferred to CYP-C from the Paediatric Oncology Group of Ontario (POGO) Networked Information System (POGONIS), which is a provincial population-based registry that includes similar data to CYP-C. For the 12 centres outside of Ontario, the data are entered directly into CYP-C. Elements captured by both databases include the following: (1) demographic variables, including sex, date of birth, postal code and race; (2) diagnostic details; (3) times to diagnosis and treatment; (4) treatment plan details, including enrollment on a therapeutic trial and whether the initial treatment plan was terminated early or completed as planned; and (5) outcomes such as relapse, second malignancy and death.

The reasons for non-enrollment have been consistently collected by CYP-C throughout the study period, whereas a standardised list has only recently been incorporated into POGONIS. Thus, description of reasons for non-enrollment was restricted to the 12 non-Ontario sites.

The CYP-C program achieves high-quality data through multiple approaches. A community of practice composed of each site's data manager was established to maximise the data quality through monthly teleconference and annual face-to-face training combined with site audits. The data were provided for the purpose of this analysis on 19 September 2016.

Statistical plan. Event-free survival was defined as time from diagnosis to relapse or death from any cause, whichever occurred first. Those without an event were censored on the date of last follow-up. Overall survival was defined as time from diagnosis to death from any cause or date of last follow-up. Survival was described for those enrolled and not enrolled on a therapeutic trial at diagnosis using the Kaplan–Meier method and compared using the log rank test.

In order to evaluate potential confounders, Cox proportional hazards models were created. The following variables were examined: (1) demographic features: age at diagnosis (1–4, 5–9 and 10–14), sex, race, and diagnostic era (<2007 *vs* ⩾2007, the approximate mid-

point); (2) Leukaemia features: initial white blood cell count (WBC) (⩾50 *vs* <50 × 10^9 l^{-1}), central nervous system (CNS) status 1 (no blasts), 2 (presence <5 μl^{-1} WBCs and cytospin positive for blasts) or 3 (CSF >5 μl^{-1} WBCs and cytospin positive for blasts), immunophenotype (B-precursor *vs* T), and cytogenetic risk group; and (3) Socioeconomic factors: kilometers to the nearest tertiary care paediatric centre and neighborhood income quintile. We also stratified analyses by National Cancer Institute (NCI) standard (age <10 years and initial WBC <50 × 10^9 l^{-1}) and high (age ⩾10 years or initial WBC ⩾50 × 10^9 l^{-1}) risk groups. Favourable cytogenetics were defined as trisomies 4 and 10 and *t*(12;21). Unfavourable cytogenetics were defined as hypodiploidy (<45 chromosomes), *t*(9;22), MLL (11q23) rearrangements, and RUNX1 (AML1) amplification.

We used postal codes at diagnosis to determine distance to the nearest tertiary care paediatric cancer centre and area-level socio-economic status by linking to the census data. Full 6 digit postal codes were available for all provinces except for British Columbia, in which 3 digit postal codes were available. Using the Statistics Canada Postal Code Conversion File software (PCCF+, Version 4J), we linked the postal code to a 2001 census dissemination area. Dissemination areas are the smallest area unit defined by Statistics Canada and include between 400 and 700 persons. Using the 2001 census, we determined income quintiles that adjust for household size and regional differences (Borugian *et al*, 2005).

Adjusted associations between enrollment on trials and survival outcomes were described using hazard ratios (HR) with 95% confidence intervals (CIs). Models adjusted for all demographic, leukaemic and socioeconomic factors separately and then together. 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, NC, USA).

RESULTS

There were 2732 identified children with ALL in CYP-C, among whom 72 had unknown enrollment status, 76 were infants<1 year of age and 15 had Burkitt's leukaemic, leaving 2569 patients available for analysis. Of the 2569 included patients, 1408 (54.8%) were enrolled on a clinical trial at diagnosis. For the 1408 enrolled on a clinical trial, 562 (39.9%) were enrolled on Children's Oncology Group protocols, 336 (23.9%) were enrolled on Dana Farber Cancer Institute ALL Consortium protocols and the remainder were others or unknown. Conversely, for the 1161 not enrolled on a trial, 506 (43.6%) were treated according to Children's Oncology Group protocols, 78 (6.7%) were treated according to Dana Farber Cancer Institute protocols and the remainder were others or unknown.

Table 1 shows the demographic, leukaemic and socioeconomic features of the study cohort by enrollment status. Those enrolled were more likely to be white, have an initial WBC<50 × 10^9 l^{-1}, CNS 2 status, B precursor immunophenotype and favourable cytogenetic features. Table 2 illustrates the reasons for non-enrollments for centres outside of Ontario and shows that the most common known reason for non-enrollment was lack of an available trial.

Event-free survival at 5 years was 89.8% ± 0.9 *vs* 84.1% ± 1.2, *P*<0.0001, for those enrolled and not enrolled on a therapeutic trial at diagnosis respectively (Figure 1). Overall survival at 5 years was 94.1% ± 0.7 *vs* 90.5% ± 1.0, *P* = 0.001 (Figure 2). Table 3 shows univariate Cox proportional hazards models evaluating factors associated with survival. Enrollment on trials was significantly associated with better EFS (HR: 0.62, 95% CI: 0.49–0.78; *P*<0.0001) and OS (HR: 0.61, 95% CI: 0.45–0.82; *P* = 0.001). When stratified by NCI risk status and presented by those enrolled *vs* not enrolled, EFS was 91.0 ± 1.0 *vs* 86.8 ± 1.3 (*P* = 0.006) for
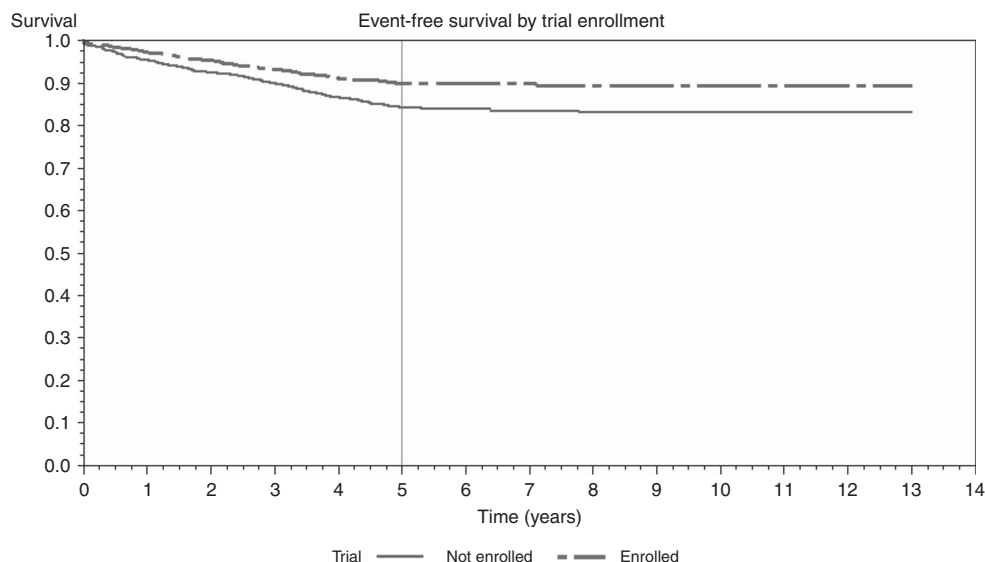
Figure 1. Event-free survival for children with acute lymphoblastic leukaemic enrolled and not enrolled on a clinical trial.
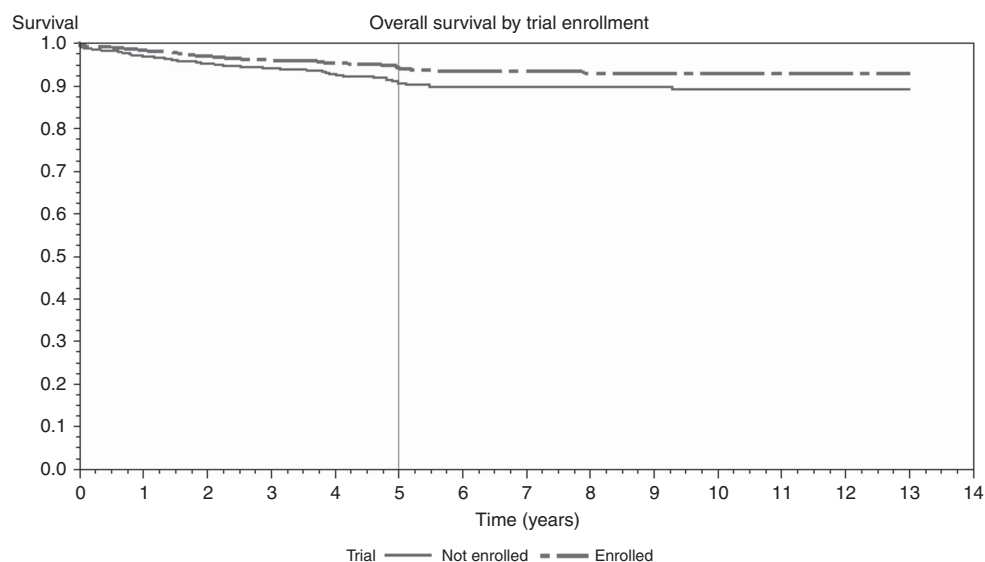

Figure 2. Overall survival for children with acute lymphoblastic leukaemic enrolled and not enrolled on a clinical trial.

standard-risk patients and was 86.9 ± 1.8 vs 78.7 ± 2.3 ($P = 0.006$) for high-risk patients, respectively. Overall survival was 96.2 ± 0.7 vs 93.4 ± 1.0 ($P = 0.014$) for standard-risk patients and was 88.5 ± 1.9 vs 84.1 ± 2.3 ($P = 0.093$) for high-risk patients.

Table 4 illustrates adjusted analyses by demographic, leukaemic and socioeconomic factors and adjustment for all factors together. In the fully adjusted model, enrollment on trials was significantly associated with better EFS (HR: 0.67, 95% CI: 0.47–0.95; $P = 0.023$) but not OS (HR: 0.69, 95% CI: 0.44–1.08; $P = 0.102$). To determine if the impact of enrollment on EFS differed by age group, an interaction term was evaluated in a multivariable model which included enrollment and age. The P-value for interaction was 0.870 suggesting a similar effect across age groups.

When examining the proportion of treatment plans terminated early rather than completed as planned, 249 out of 1408 (17.7%) for those enrolled were terminated early compared to 156 out of 1161 (13.4%) for those not enrolled ($P = 0.004$). When the analysis was restricted to children with ALL treated according to Children's Oncology Group trials, enrollment was associated with better EFS (HR: 0.61, 95% CI: 0.42–0.88; $P = 0.008$) and OS (HR: 0.46, 95%

CI: 0.27–0.76; $P = 0.003$). This benefit was not seen when the analysis was restricted to children treated according to Dana Farber Cancer Institute trials; enrollment was not associated with better EFS (HR: 0.75, 95% CI: 0.35–1.63; $P = 0.475$) or OS (HR: 1.11, 95% CI: 0.39–3.21; $P = 0.843$).

DISCUSSION

We found that enrollment on a therapeutic clinical trial at initial leukaemic diagnosis was independently associated with better EFS for children newly diagnosed with ALL after adjustment for demographic, leukaemic and socioeconomic factors. Improved EFS was also seen when stratified by NCI risk status. This information may be important to families and clinicians when deciding whether to enroll on a clinical trial at diagnosis.

Our results are discordant with (Koschmann et al, 2010) who evaluated the trial effect among paediatric ALL patients treated at Seattle Children's Hospital from 1997 to 2005. They failed to demonstrate an EFS advantage to participation in studies However,

Table 1. Demographics of acute lymphoblastic leukaemia study population by enrollment status

Characteristics	Total $N = 2569$	Enrolled ($N = 1408$)	Not enrolled ($N = 1161$)	Percent enrolled	P-value[a]
Demographic features					
Age at diagnosis					0.501
1–4 years	1411 (54.9%)	788 (56.0%)	623 (53.7%)	55.8	
5–9 years	732 (28.5%)	393 (27.9%)	339 (29.2%)	53.7	
10–14 years	426 (16.6%)	227 (16.1%)	199 (17.1%)	53.3	
Male sex	1451 (56.5%)	810 (57.5%)	641 (55.2%)	55.8	0.238
Race					<0.0001
White	1752 (68.2%)	1051 (74.6%)	701 (60.4%)	60.0	
Asian	306 (11.9%)	132 (9.4%)	174 (15.0%)	43.1	
Arab/West Asian	48 (1.9%)	24 (1.7%)	24 (2.1%)	50.0	
Aboriginal	73 (2.8%)	39 (2.8%)	34 (2.9%)	53.4	
Black	54 (2.1%)	28 (2.0%)	26 (2.2%)	51.9	
Latin American	37 (1.4%)	17 (1.2%)	20 (1.7%)	45.9	
Other	52 (2.0%)	25 (1.8%)	27 (2.3%)	48.1	
Unknown	247 (9.6%)	92 (6.5%)	155 (13.4%)	37.2	
Diagnostic era					0.429
<2007	1280 (49.8%)	712 (50.6%)	568 (48.9%)	55.6	
≥2007	1289 (50.2%)	696 (49.4%)	593 (51.1%)	54.0	
Leukaemia features					
Initial white blood cell count					0.002
$<50 \times 10^9$ l^{-1}	2115 (82.3%)	1190 (84.5%)	925 (79.7%)	56.3	
$\geqslant 50 \times 10^9$ l^{-1}	454 (17.7%)	218 (15.5%)	236 (20.3%)	48.0	
CNS status					0.002
CNS1	2292 (89.2%)	1237 (87.9%)	1055 (90.9%)	54.0	
CNS2	217 (8.4%)	142 (10.1%)	75 (6.5%)	65.4	
CNS3	53 (2.1%)	28 (2.0%)	25 (2.2%)	52.8	
Unknown	7 (0.3%)	1 (0.1%)	6 (0.5%)	14.3	
Immunophenotype					0.0006
B-precursor	1313 (51.1%)	810 (57.5%)	503 (43.3%)	61.7	
T	159 (6.2%)	75 (5.3%)	84 (7.2%)	47.2	
Unknown	1097 (42.7%)	523 (37.1%)	574 (49.4%)	47.7	
Cytogenetic risk group					0.039
Favourable	779 (30.3%)	454 (32.2%)	325 (28.0%)	58.3	
Standard	1673 (65.1%)	897 (63.7%)	776 (66.8%)	53.6	
Unfavourable	117 (4.6%)	57 (4.0%)	60 (5.2%)	48.7	
Socioeconomic factors					
Median Km to nearest tertiary care centre (interquartile range)	29.3 (12.7–104.5)	30.1 (12.5–106.6)	28.7 (13.3–99.3)		0.689
Income quintile					0.485
1 (lowest)	486 (18.9%)	254 (18.0%)	232 (20.0%)	52.3	
2	479 (18.6%)	259 (18.4%)	220 (18.9%)	54.1	
3	517 (20.1%)	298 (21.2%)	219 (18.9%)	57.6	
4	537 (20.9%)	292 (20.7%)	245 (21.1%)	54.4	
5 (highest)	502 (19.5%)	282 (20.0%)	220 (18.9%)	56.2	
Missing	48	23	25		

[a]P-value by Chi square test for categorical variables and by Wilcoxon rank sum test for continuous variable.

Table 2. Reasons for non-enrollment on trials in 12 non-Ontario institutions

	Total ($N = 595$)
No available trial[a]	319 (53.6%)
Language barrier, trial not offered	9 (1.5%)
Not eligible for any trial[a]	54 (9.1%)
Physician choice	24 (4.0%)
Refused therapy	5 (0.8%)
Refused to participate in trial	62 (10.4%)
Other	14 (2.4%)
Unknown	108 (18.2%)

[a]No available trial suggests that a trial was not available for a specific disease. In contrast, not eligible for any trial suggests that a trial was available for a patient's disease but the patient did not meet that trial's eligibility criteria.

this report was limited since it included only a single centre in the United States. Further, the sample size consisted of only 322 patients (with 48.8% enrolment).

Reasons why enrollment on trials could improve EFS include the following: (1) Treatment effect, in which the interventions being evaluated result in better outcomes compared with standard approaches; (2) Participation effect where enrollment in the trial results in better outcomes due to the effect of the protocol, changes in healthcare professional behavior, changes in patient/family behavior or a placebo effect; and (3) Confounding, if patients enrolled on trials are systematically different than patients not enrolled on trials. The adjusted analyses were important as those enrolled on trials, when compared to those not enrolled, had generally favourable features such as low initial WBC, B precursor immunophenotype and favourable risk cytogenetics. By taking into consideration confounding using several approaches, our study suggests that improved EFS may be the result of the interventions being evaluated in these studies and is

Table 3. Impact of trial enrollment on event-free and overall survival[a]				
	Event-free survival		Overall survival	
Characteristics	HR (95% CI)	P-value	HR (95% CI)	P-value
Enrollment on trial				
Enrolled	0.62 (0.49–0.78)	<0.0001	0.61 (0.45–0.82)	0.001
Demographic features				
Age at diagnosis		<0.0001		<0.0001
1–4 years	REF		REF	
5–9 years	1.61 (1.24–2.09)	0.0004	1.82 (1.28–2.58)	0.0009
10–14 years	1.92 (1.43–2.58)	<0.0001	2.54 (1.74–3.70)	<0.0001
Sex				
Male	1.32 (1.05–1.68)	0.020	1.41 (1.03–1.93)	0.031
Race		0.213		0.131
White	REF		REF	
Asian	0.73 (0.50–1.09)	0.124	0.73 (0.43–1.22)	0.227
Arab/West Asian	1.17 (0.55–2.48)	0.690	0.57 (0.14–2.29)	0.426
Aboriginal	1.55 (0.89–2.71)	0.125	1.92 (0.97–3.77)	0.060
Black	1.04 (0.49–2.21)	0.919	0.50 (0.12–2.03)	0.502
Latin American	0.22 (0.03–1.53)	0.125	0.40 (0.06–2.83)	0.356
Other	0.45 (0.14–1.39)	0.164	0.51 (0.13–2.08)	0.350
Unknown	0.94 (0.61–1.46)	0.795	1.44 (0.88–2.33)	0.144
Diagnostic era				
Prior to 2007	1.87 (1.46–2.40)	<0.0001	1.72 (1.24–2.37)	0.001
Leukaemia features				
Initial white blood cell count				
$\geqslant 50 \times 10^9 \, l^{-1}$	1.88 (1.45–2.45)	<0.0001	2.81 (2.04–3.86)	<0.0001
CNS status		0.029		0.0009
CNS 1	REF			
CNS 2	1.20 (0.81–1.79)	0.360	1.58 (0.98–2.55)	0.063
CNS 3	1.46 (0.69–3.09)	0.325	1.47 (0.54–3.97)	0.449
Immunophenotype				
B-precursor	0.47 (0.32–0.70)	0.0002	0.33 (0.21–0.52)	<0.0001
Cytogenetic risk group		<0.0001		<0.0001
Favourable	0.36 (0.25–0.50)	<0.0001	0.27 (0.16–0.45)	<0.0001
Standard	REF		REF	
Unfavourable	2.61 (1.83–3.71)	<0.0001	3.46 (2.29–5.21)	<0.0001
Socioeconomic factors				
Nearest tertiary care centre				
Kilometers	1.00 (1.00–1.00)	0.824	1.00 (1.00–1.00)	0.183
Income quintile		0.636		0.555
1 (lowest)	REF		REF	
2	0.86 (0.60–1.23)	0.412	1.16 (0.73–1.83)	0.530
3	0.92 (0.65–1.31)	0.648	0.89 (0.55–1.43)	0.620
4	0.77 (0.53–1.10)	0.147	0.89 (0.55–1.42)	0.617
5 (highest)	0.82 (0.57–1.17)	0.277	0.78 (0.47–1.28)	0.327

Abbreviations: CI = confidence interval; CNS = central nervous system; HR = hazard ratio; REF = reference.
[a]Univariate Cox proportional hazards model in which a HR < 1 indicates better survival.

consistent with improved outcomes in paediatric ALL with successive clinical trials (Pui *et al*, 2015). However, we cannot exclude that participation effect may have a role as well. If improved EFS is the result of interventions being evaluated, this finding may not apply to trials examining de-escalation of therapy.

We also found that when patients were treated with COG protocols, patients enrolled had better outcomes compared to those not enrolled, whereas a similar pattern was not seen among those treated according to Dana Farber Cancer Institute protocols. This finding may be related to either the interventions being evaluated in specific trials or may be related to the smaller number of children receiving Dana Farber Cancer Institute studies. We also found that those enrolled on trials were more likely to terminate the treatment plan early compared to those not enrolled on trials. This finding may be an artefact of how the data were collected since if patients enrolled on trials were taken off protocol therapy but continued to follow the same treatment protocol, they were designated as terminating treatment early and starting a new treatment plan as a non-registered patient.

Our results were less definitive regarding whether enrollment on trials improves OS and such an effect is difficult to demonstrate in a disease with high success rates in general. While we found that OS was not improved in the adjusted models, it should be noted that the HR favoured enrollment and that power was limited given excellent survival. Thus, combining the CYP-C data set with other population-based registries may help us understand whether enrollment on trials can reduce mortality.

The strengths of this study are its population-based nature and careful collection of confounders, including leukaemic and socio-economic factors. Other strengths are the high quality of data and common health care system, which provides universal healthcare. However, these results must be interpreted in light of its limitations. First, potentially important covariates were not available such as minimal residual disease (MRD) status. Second,

Table 4. Impact of enrollment on trials on event-free and overall survival in adjusted models[a]

Characteristics	Event-free survival		Overall survival	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Variables included in multiple regression				
Demographic: age, gender, ethnicity, era	0.60 (0.48–0.76)	<0.0001	0.61 (0.45–0.82)	0.001
Leukaemia: white count, CNS status, immunophenotype, cytogenetics	0.72 (0.53–0.99)	0.040	0.75 (0.50–1.13)	0.163
Socioeconomic: distance and income quintile	0.64 (0.50–0.82)	0.0003	0.63 (0.45–0.86)	0.004
Demographic, leukaemic and socioeconomic factors	0.67 (0.47–0.95)	0.023	0.69 (0.44–1.08)	0.102

Abbreviations: CI = confidence interval; CNS = central nervous system; HR = hazard ratio.
[a]Multiple Cox proportional hazards model in which the estimates reflect the adjusted effect of enrollment on trials where a HR<1 indicates better survival.

we did not include adolescent and young adult patients (AYA) in our study. This is important as several studies have identified that AYA patients have lower rates of enrollment on clinical trials (Bleyer, 2002; Downs-Canner and Shaw, 2009; Aristizabal *et al*, 2015). Third, we lacked immunophenotype information for over 40% of children related to how POGO classifies ALL; this missing data affected the power of analyses, which adjusted for leukaemic-related factors. Finally, we used a census based measure of family income as individually reported data from the family were not available at the population level.

In conclusion, EFS was significantly better in children with ALL enrolled on a clinical trial. Future research should identify barriers to clinical trial enrollment for children with ALL.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

The study received Research Ethics Board approval from the coordinating site (The Hospital for Sick Children). For sites outside of Ontario, Research Ethics Board approval was obtained for collection of CYP-C data. For the five Ontario sites, the requirement for Research Ethics Board approval was waived given the Paediatric Oncology Group of Ontario's status as a prescribed 45 Entity under the Personal Health Information Protection Act, 2004. This status allows the Paediatric Oncology Group of Ontario to be a custodian of personal health information for the province. The requirement for informed consent and assent were waived given the retrospective nature of the study.

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