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Regular Article

HEMATOPOIESIS AND STEM CELLS

Patient-reported outcomes in survivors of childhood hematologic malignancies with hematopoietic stem cell transplant

Hsiu-Ju Yen,[1] Hesham M. Eissa,[2] Neel S. Bhatt,[3] Sujuan Huang,[4] Matthew J. Ehrhardt,[5,6] Nickhill Bhakta,[5-7] Kirsten K. Ness,[5] Kevin R. Krull,[5,8] D. Kumar Srivastava,[4] Leslie L. Robison,[5] Melissa M. Hudson,[5,6] and I-Chan Huang[5]

[1]Department of Pediatrics, Taipei Veterans General Hospital and National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.; [2]Pediatric Department, Children's Hospital Colorado, Aurora, CO; [3]Pediatric Oncology Program, Fred Hutchinson Cancer Research Center, Seattle, WA; and [4]Department of Biostatistics, [5]Department of Epidemiology & Cancer Control, [6]Department of Oncology, [7]Department of Global Pediatric Medicine, and [8]Department of Psychology, St. Jude Children's Research Hospital, Memphis, TN

KEY POINTS

- Occurrence of chronic health conditions, not transplant receipt, is related to symptom prevalence in pediatric hematologic malignancy survivors.

Patient-reported outcomes among survivors of pediatric hematopoietic stem cell transplant (HSCT) are understudied. We compared symptom prevalence, health-related quality of life (HRQOL), and risk factors in adult survivors of childhood hematologic malignancies treated with HSCT to those treated with conventional therapy and noncancer controls. Survivors of childhood hematologic malignancies (HSCT N = 112 [70% allogeneic, 30% autologous]; conventionally treated N = 1106) and noncancer controls (N = 242) from the St. Jude Lifetime Cohort Study completed surveys assessing 10 symptom domains and SF-36 HRQOL summary scores. Chronic health conditions (CHCs) were validated by clinical assessment. Multivariable logistic regression reveals that compared with noncancer controls, HSCT survivors endorsed a significantly higher symptom prevalence in sensation (OR = 4.7, 95% confidence interval [CI], 2.6-8.4), motor/movement (OR = 4.3, 95% CI, 1.6-11.0), pulmonary (OR = 4.6, 95% CI, 1.8-11.8), and memory domains (OR = 4.8, 95% CI, 2.5-9.2), and poorer physical HRQOL (OR = 6.9, 95% CI, 2.8-17.0). HSCT and conventionally treated survivors had a similar prevalence of all symptom domains and HRQOL (all $P > .05$); however, HSCT survivors had a significantly higher cumulative prevalence for specific symptoms: double vision ($P = .04$), very dry eyes ($P < .0001$), and trouble seeing when wearing glasses ($P < .0001$). Occurrence of organ-specific CHCs, instead of transplant receipt, was significantly associated with a higher prevalence of all symptom domains (all $P < .05$) in adult survivors of childhood cancer, except for pain and anxiety domains. This study found that patient-reported outcomes were equally impaired between HSCT and conventionally treated survivors, but poorer in both groups compared with noncancer controls. Poor patient-reported outcomes in all survivors of childhood hematologic malignancies correlated with the presence of CHCs, whether treated with conventional therapy or HSCT. (*Blood.* 2020;135(21):1847-1858)

Introduction

Hematopoietic stem cell transplant (HSCT) is used for some children and adolescents with hematologic malignancies.[1,2] Progress in transplant technology (eg, donor matching, alternative donor source, conditioning regimens), and supportive care have significantly improved the post-HSCT survival.[3,4] However, survivors are at risk for developing chronic graft-versus-host disease (GVHD) and other chronic health conditions (CHCs) that may contribute to late morbidity.[3,5-8] The number and severity of CHCs increase in the years following therapy completion, adversely affecting the quality and duration of their survival.[7,9]

Assessing patient-reported outcomes (eg, symptom prevalence and health-related quality of life [HRQOL]) provides unique health information perceived by cancer survivors that is complementary to traditional clinical end points (eg, disease stage, survival).[10-12] Several studies have explored symptom phenotypes and HRQOL in survivors of adult-onset cancer,[11] pediatric cancer,[12-16] and adults treated with HSCT.[10,17,18] We previously reported that ~80% of adult survivors of childhood cancer experienced multiple symptoms decades after a diagnosis of pediatric cancers.[12] We also observed that survivors, compared with individuals without cancer history, had a higher symptom burden that was associated with more CHCs and impaired HRQOL.[11] Given the elevated risk of CHCs in survivors of pediatric HSCT,[7,9] routine symptom assessment becomes clinically important as symptom phenotypes may indicate the new onset of adverse health problems.

Studies investigating symptom and HRQOL issues in pediatric HSCT survivors are limited by short follow-up duration (often

Table 1. Characteristics of study participants

Characteristics	HSCT survivors (N = 112)	Conventional therapy survivors (N = 1106)	Noncancer controls (N = 242)	HSCT survivors vs conventional therapy survivors	HSCT survivors vs noncancer controls
				P	*P*
Age (y) at survey, mean ± SD (range)	28.4 ± 5.9 (18.8-43.2)	29.2 ± 6.2 (18.3-47.6)	35.1 ± 10.4 (18.1-70.0)	.132	<.001
Sex, n (%)				.741	.555
Female	55 (49.1)	525 (47.5)	140 (52.6)		
Male	57 (50.9)	581 (52.5)	126 (47.4)		
Race/ethnicity, n (%)				.026	.03
White, non-Hispanic	83 (74.1)	914 (82.6)	203 (83.9)		
Other	29 (25.9)	192 (17.4)	39 (16.1)		
Diagnosis, n (%)				<.001	NA
Acute lymphoblastic leukemia	23 (20.5)	649 (58.7)	NA		
Acute myeloid leukemia	44 (39.3)	42 (3.8)	NA		
Lymphoma (Hodgkin, non-Hodgkin)	18 (16.0)	413 (37.3)	NA		
Other	27 (24.1)	2 (0.2)	NA		
Age (y) at diagnosis, mean ± SD (range)	9.8 ± 5.3 (0.5-18.8)	9.4 ± 5.5 (0.2-21.8)	NA	.425	NA
Time (y) since diagnosis, mean ± SD (range)	18.5 ± 4.2 (11.3-28.5)	19.9 ± 5.1 (10.5-32.9)	NA	.002	NA
Treatment era, n (%)				<.001	NA
1980-1989	24 (21.4)	503 (45.5)	NA		
1990-1999	76 (67.9)	502 (45.4)	NA		
2000 and after	12 (10.7)	101 (9.1)	NA		
Education, n (%)				.039	.559
<College	63 (56.3)	730 (66.0)	127 (52.9)		
≥College	49 (43.8)	376 (34.0)	113 (47.1)		
Annual household income, n (%)				.553	.016
<$20 000	62 (59.0)	568 (54.1)	93 (39.6)		
$20 000-$39 999	22 (21.0)	241 (23.0)	46 (19.6)		
$40 000-$59 999	9 (8.6)	134 (12.8)	43 (18.3)		
>$60 000	12 (11.4)	107 (10.2)	53 (22.6)		
Marital status, n (%)				.017	<.001
Single/divorced/other	72 (64.3)	580 (52.4)	76 (31.4)		
Married/living with partner	40 (35.7)	526 (47.6)	166 (68.6)		
Health insurance, n (%)				.713	.036
Insured	84 (75.0)	811 (73.5)	204 (84.3)		
Uninsured	28 (25.0)	294 (26.6)	38 (15.7)		
Independent living, n (%)				.009	<.001
Living independently	63 (56.3)	755 (68.3)	205 (84.7)		
Live dependently	49 (43.8)	349 (31.6)	37 (15.3)		

NA, nonapplicable.

*Among 25 survivors having chronic GVHD, 23 with past and 2 with active chronic GVHD at the time of study.

†Intensity of transplant experience: low (autologous), intermediate (allogeneic without the occurrence of chronic GVHD), and severe (allogeneic with the occurrence of chronic GVHD).

Table 1. (continued)

Characteristics	HSCT survivors (N = 112)	Conventional therapy survivors (N = 1106)	Noncancer controls (N = 242)	HSCT survivors vs conventional therapy survivors	HSCT survivors vs noncancer controls
				P	*P*
Radiation treatment, n (%)					
Total body irradiation	82 (73.1)	0 (0)	NA	<.001	NA
Cranial/spinal	9 (8.0)	278 (25.1)	NA	<.001	NA
Chest	2 (1.8)	17 (1.5)	NA	.840	NA
Pelvic/abdominal	4 (3.6)	35 (3.2)	NA	.816	NA
Chemotherapy, n (%)					
Alkylators	111 (99.1)	743 (67.2)	NA	<.001	NA
Anthracyclines	87 (77.7)	941 (85.1)	NA	.04	NA
Antimetabolites	111 (99.1)	955 (86.4)	NA	<.001	NA
Dexamethasone	35 (31.3)	234 (21.2)	NA	.014	NA
Epipodophyllotoxin	699 (63.2)	80 (71.4)	NA	.084	NA
High-dose methotrexate	37 (33.0)	654 (59.1)	NA	<.001	NA
Prednisone	46 (41.1)	939 (84.9)	NA	<.001	NA
Vincristine	45 (40.2)	973 (88.0)	NA	<.001	NA
Type of HSCT, n (%)					
Allogeneic	79 (70.1)	NA	NA	NA	NA
Autologous	33 (29.5)	NA	NA	NA	NA
Chronic GVHD among allogeneic HSCT survivors, n (%)					
Yes*	25 (31.6)	NA	NA	NA	NA
No	54 (68.4)	NA	NA	NA	NA
Intensity of transplant experience, n (%)†					
Low	33 (29.5)	NA	NA	NA	NA
Intermediate	52 (46.4)	NA	NA	NA	NA
Severe	27 (24.1)	NA	NA	NA	NA
Relapse, n (%)				<.001	
Yes	24 (21.4)	505 (45.7)	NA		NA
No	88 (78.6)	601 (54.3)	NA		NA
Second tumor, n (%)				.004	
Yes	28 (25.0)	141 (12.8)	NA		NA
No	84 (75.0)	965 (87.3)	NA		NA

NA, nonapplicable.

*Among 25 survivors having chronic GVHD, 23 with past and 2 with active chronic GVHD at the time of study.

†Intensity of transplant experience: low (autologous), intermediate (allogeneic without the occurrence of chronic GVHD), and severe (allogeneic with the occurrence of chronic GVHD).

5-15 years),[19-22] assessment of limited symptom domains (mostly pain or fatigue),[23,24] or inclusion of small[2,20,22,24] or heterogeneous[23-25] samples. Although symptoms reflect the manifestation of CHCs, few studies have evaluated the association of CHCs and patient-reported outcomes in HSCT survivors. Therefore, conflicting findings have been reported when comparing symptom prevalence between survivors of pediatric hematologic malignancy treated with and without HSCT. Some studies noted a similar prevalence of pain,[22,23] fatigue,[21] and anxiety/depression,[22,23] whereas others reported higher prevalence of pain in HSCT survivors compared with conventionally treated survivors.[21,24]

The first objective of this study was to compare symptom prevalence and HRQOL in long-term (≥20 years since diagnosis) survivors of childhood hematologic malignancies treated with HSCT to survivors treated with conventional therapies and noncancer controls, respectively. We hypothesized that HSCT survivors would in general have a higher symptom prevalence and poorer HRQOL compared with conventional therapy survivors and noncancer controls. The second objective was to identify risk factors for elevated symptom prevalence and poor HRQOL, with a focus on the influence of CHCs. We hypothesized that associations of higher symptom prevalence and poorer HRQOL related to HSCT experience (ie, receipt of

HSCT vs conventional therapy) would be significantly related to the occurrence of CHCs, particularly for associations of symptom prevalence with CHCs from the same organ system. In contrast to previous studies that collected CHC data through self-reports,[20,22,26,27] we conducted medical assessments to evaluate CHCs.[28]

Patients and methods

Study sample

This cross-sectional study used data collected from adult survivors of childhood cancer enrolled in the St. Jude Lifetime Cohort Study, a retrospective cohort study with prospective follow-ups established to investigate etiologies of late effects related to pediatric cancer therapies.[28,29] The study sample consisted of cancer survivors who received conventional therapy for a hematologic cancer, a subgroup of whom also underwent HSCT. Survivors received comprehensive medical assessments per the Children's Oncology Group Long-Term Follow-up Guidelines.[30,31] Additionally, community controls having no history of cancer were included as a comparison group.

Data collection

Eligible survivors were: (1) ≥18 years of age at the time of participation; (2) treated for a hematologic malignancy, including acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and myelodysplastic syndromes, at St. Jude Children's Research Hospital; and (3) had survived ≥10 years after the completion of cancer therapies between January 1, 1982, and June 30, 2005. Eligible noncancer controls were: (1) ≥18 years of age at the time of participation; (2) non–first-degree relatives or friends of St. Jude patients, or any volunteer not associated with St. Jude; and (3) not treated for a childhood cancer.

Among 1965 potentially eligible participants, 1218 survivors (112 with HSCT [70% allogeneic, 30% autologous] and 1106 with conventional therapy only) and 242 noncancer controls who completed questionnaires and medical assessments at St. Jude Children's Research Hospital were included (supplemental Figure 1, available on the *Blood* Web site). The study protocol was approved by St. Jude's institutional review board, and all participants provided written informed consent for evaluations.

Measurement

Symptom assessments comprised 37 items recommended by the Children's Oncology Group Long-Term Follow-up Guidelines[31] that were used in our previous publication.[12] Items assessed 10 domains: sensation (8 items), motor/movement (4 items), cardiac symptoms (3 items), pulmonary symptoms (2 items), pain (4 items), fatigue (2 items), nausea (1 item), memory (1 item), anxiety (6 items), and depression (6 items) (supplemental Table 1). The presence of any symptom item within a specific domain indicated presence of that symptom domain. The Medical Outcomes Study 36-Item Short-Form Health Survey was used to measure HRQOL. Physical and mental component summary scores (PCS and MCS) were calculated and normalized to a mean of 50 and a standard deviation (SD) of 10. A threshold ≤40 (1 SD below the norm) was used to indicate poor physical and mental HRQOL.

Medical assessment data were used to categorize 168 specific CHCs using a modified Common Terminology Criteria for Adverse Events (CTCAE) grading as asymptomatic/mild (grade 1), moderate (grade 2), severe/disabling (grade 3), or life-threatening (grade 4).[28] CHCs were dichotomized as at least severe (grades 3-4) or not (no diagnosed condition or grades 1-2). This study focused on 7 CHC groups that were found to be more prevalent among survivors treated with HSCT compared with conventional therapy, including cardiovascular, endocrine, gastrointestinal, neurological, ocular, pulmonary, and reproductive disorders.[7] A specific CHC group was considered as present if any condition under that group was present.

Important risk factors contributing to symptom presence and poor HRQOL were examined, including sociodemographic variables and cancer-/HSCT-related treatments. Sociodemographic variables were self-reported, including sex, race/ethnicity (white, non-Hispanic vs other), educational attainment (below college vs college or above), and marital status (married/living with a partner vs single/divorced/other status). Cancer therapy details were abstracted from medical records inclusive of years since cancer diagnosis, type of HSCT (autologous vs allogeneic), type and cumulative dose of chemotherapy and radiation therapy, and transplant-related variables (disease status at transplant and intensity of transplant experience). Disease status was classified as first complete remission, second or subsequent complete remission, and relapsed or progression. Intensity of transplant experience was classified as low (autologous), intermediate (allogeneic without the occurrence of chronic GVHD), and severe (allogeneic with the occurrence of chronic GVHD).[17]

Statistical analysis

Student *t* and χ^2 tests were conducted to compare differences in symptom prevalence and poor HRQOL for HSCT vs conventionally treated survivors and for HSCT survivors vs noncancer controls. Cumulative prevalence of specific symptoms and HRQOL at the domain and item levels were estimated by referring the time since cancer diagnosis to the presentation of individual symptom items or domains, and poor HRQOL at the time of survey.[11] Discrepancy in cumulative prevalence rates between HSCT and conventionally treated survivors were also compared. Multivariable logistic regression models were performed to estimate the odds of symptom prevalence and poor HRQOL for HSCT vs conventional therapy survivors, and for HSCT vs noncancer controls with an adjustment for the previously mentioned risk factors. In this modeling, cancer therapy was not included because we (1) aimed to identify risk factors of poor patient-reported outcomes using a parsimonious model and (2) hypothesized that the occurrence of CHCs has direct effects on patient-reported outcomes, whereas cancer therapy has indirect effects on patient-reported outcomes through the influence of CHCs. However, we also conducted additional analysis by adding therapy variables to the parsimonious model to evaluate robustness of the findings among 2 models. Additionally, a multivariable logistic regression was performed to calculate the odds of symptom prevalence and poor HRQOL for allogeneic vs autologous survivors. Multivariable logistic regression was also performed to test associations of the aforementioned HSCT-related variables with symptom prevalence and poor HRQOL among HSCT survivors only. All analyses were performed using SAS v9.4. Statistically significant differences were decided by $P < .05$ (2-sided).

Table 2. Prevalence of symptom domains and poor HRQOL among overall HSCT survivors, conventional therapy survivors, and noncancer controls

Symptoms and HRQOL	HSCT survivors	Conventional therapy survivors	Noncancer controls	HSCT survivors vs conventional therapy survivors	HSCT survivors vs noncancer controls
	n (%)	n (%)	n (%)	OR (95% CI)*	OR (95% CI)*
Symptom prevalence					
Sensation abnormalities	44 (39.3)	365 (33.0)	45 (18.6)	1.5 (1.0-2.3)	4.7 (2.6-8.4)
Motor/movement problems	14 (12.5)	149 (13.5)	8 (3.3)	1.0 (0.5-1.8)	4.3 (1.6-11.0)
Cardiac symptoms	15 (13.4)	150 (13.6)	16 (6.6)	1.0 (0.6-1.8)	2.5 (1.1-5.6)
Pulmonary symptoms	15 (13.4)	152 (13.7)	9 (3.7)	1.0 (0.6-1.8)	4.6 (1.8-11.8)
Pain	72 (64.3)	819 (74.1)	159 (65.7)	0.7 (0.4-1.0)	1.4 (0.8-2.3)
Fatigue	15 (13.4)	195 (17.6)	18 (7.4)	0.7 (0.4-1.4)	3.1 (1.4-7.0)
Nausea	15 (13.4)	152 (13.7)	27 (11.2)	1.0 (0.6-1.8)	1.3 (0.7-2.7)
Memory problems	32 (28.6)	276 (25.0)	19 (7.9)	1.2 (0.8-1.9)	4.8 (2.5-9.2)
Anxiety	33 (29.5)	386 (34.9)	44 (18.2)	0.8 (0.5-1.3)	2.1 (1.2-3.6)
Depression	27 (24.1)	341 (30.8)	45 (18.6)	0.8 (0.5-1.2)	1.7 (0.9-2.9)
Multiple (≥2) symptoms	65 (63.7)	648 (61.9)	88 (36.8)	1.1 (0.7-1.7)	3.0 (1.9-4.9)
Poor HRQOL					
PCS ≤40	19 (17.0)	156 (14.1)	13 (5.4)	1.5 (0.9-2.5)	6.9 (2.8-17.0)
MCS ≤40	20 (17.9)	252 (22.8)	35 (14.5)	0.8 (0.5-1.3)	1.5 (0.5-2.9)

CI, confidence interval; MCS, mental component summary; OR, odds ratio; PCS, physical component summary.

*Age/sex-adjusted ORs.

Results

Table 1 summarizes the characteristics of study participants. The mean ages at assessment among survivors treated with HSCT, those treated with conventional therapy, and noncancer controls were 28.4, 29.2, and 35.1 years, respectively. The mean years since cancer diagnosis was 18.5 for survivors treated with HSCT and 19.9 for those treated with conventional therapy.

Table 1 also reports that a majority of HSCT survivors (67.9%) were treated between 1990 and 1999, and near equal numbers

Table 3. Prevalence of chronic health conditions among overall HSCT survivors, conventional therapy survivors, and noncancer controls

Chronic health conditions (CTCAE grades ≥3)	HSCT survivors	Conventional therapy survivors	Noncancer controls	HSCT survivors vs conventional therapy survivors	HSCT survivors vs noncancer controls
	n (%)	n (%)	n (%)	OR (95% CI)*	OR (95% CI)*
Cardiovascular	17 (15.2)	89 (8.1)	12 (5.0)	2.3 (1.3-4.1)	7.4 (2.8-19.3)
Endocrine	29 (25.9)	422 (38.2)	91 (37.6)	0.6 (0.4-0.9)	0.8 (0.5-1.3)
Gastrointestinal	20 (17.9)	117 (10.6)	23 (9.5)	2.1 (1.2-3.6)	3.6 (1.7-7.7)
Neurology	9 (8.1)	83 (7.5)	15 (6.2)	1.1 (0.6-2.3)	1.6 (0.6-4.1)
Ocular	22 (19.6)	12 (1.1)	2 (0.8)	23.2 (11.0-48.7)	47.2 (9.6-231.7)
Pulmonary	17 (15.2)	60 (5.4)	17 (7.0)	3.5 (1.9-6.3)	2.8 (1.3-6.1)
Reproductive	60 (53.6)	203 (18.4)	18 (7.4)	5.6 (3.7-8.4)	37.1 (16.0-86.0)
Multiple (≥2) conditions	53 (47.3)	241 (21.8)	38 (15.7)	3.2 (2.2-4.8)	4.8 (2.9-8.0)

*Age/sex-adjusted ORs.

Table 4. Multivariable logistic regression for risks of symptom domain prevalence and poor HRQOL between overall HSCT and conventional therapy survivors by accounting for chronic health conditions

Risk factors	Sensation abnormalities OR (95% CI)	Motor/ movement problems OR (95% CI)	Cardiac symptoms OR (95% CI)	Pulmonary symptoms OR (95% CI)	Pain OR (95% CI)	Fatigue OR (95% CI)
Treatment group Overall HSCT vs conventional therapy survivors*	1.2 (0.8-2.0)	1.0 (0.5-1.9)	0.9 (0.4-1.7)	1.0 (0.5-1.9)	0.5 (0.3-0.8)	0.7 (0.3-1.3)
Age at survey	1.1 (1.0-1.1)	1.1 (1.0-1.1)	1.1 (1.0-1.1)	1.1 (1.0-1.1)	1.0 (1.0- 1.1)	1.1 (1.0-1.1)
Sex Female vs male*	1.3 (1.1-1.7)	1.5 (1.0-2.1)	2.4 (1.7-3.5)	1.5 (1.0-2.0)	1.7 (1.3-2.3)	1.9 (1.4-2.5)
Race/ethnicity White, non-Hispanic vs other*	1.4 (1.0-2.0)	1.0 (0.6-1.5)	0.9 (0.6-1.4)	0.8 (0.5-1.2)	1.3 (0.9-1.8)	1.1 (0.7-1.7)
Education <College vs ≥college*	1.3 (1.0-1.8)	1.7 (1.2-2.6)	1.5 (1.1-2.3)	1.6 (1.1-2.3)	1.8 (1.3-2.4)	2.3 (1.6-3.3)
Marital status Single/divorced/other vs married/living with partner*	1.0 (0.8-1.4)	1.6 (1.1-2.3)	1.0 (0.7-1.4)	1.7 (1.2-2.4)	0.8 (0.6-1.1)	0.9 (0.7-1.3)
Cardiovascular†	1.3 (0.8-1.9)	1.2 (0.7-2.1)	3.0 (1.8-4.9)	1.2 (0.7-2.1)	1.5 (0.9-2.7)	1.2 (0.7-2.0)
Endocrine†	1.4 (1.1-1.8)	1.9 (1.4-2.7)	1.0 (0.7-1.4)	1.2 (0.9-1.8)	1.4 (1.0-1.8)	1.5 (1.1-2.1)
Gastrointestinal†	1.3 (0.9-1.9)	1.4 (0.9-2.3)	1.2 (0.7-2.0)	1.5 (0.9-2.4)	1.3 (0.8-2.1)	1.2 (0.7-1.9)
Neurology†	1.9 (1.2-3.1)	3.3 (2.0-5.5)	1.4 (0.8-2.5)	1.9 (1.1-3.2)	1.3 (0.8-2.4)	1.9 (1.2-3.2)
Ocular†	2.2 (1.0-4.8)	2.7 (1.1-6.9)	1.0 (0.3-2.9)	0.5 (0.1-1.7)	2.3 (0.9-6.0)	2.3 (0.9-5.6)
Pulmonary†	1.0 (0.6-1.7)	0.9 (0.4-1.7)	3.0 (1.7-5.3)	2.5 (1.4-4.3)	1.8 (0.9-3.6)	1.0 (0.5-1.8)
Reproductive†	1.3 (1.0-1.8)	0.8 (0.5-1.2)	0.9 (0.6-1.4)	1.0 (0.6-1.5)	1.4 (1.0-2.0)	1.4 (1.0-2.1)

Risk factors	Nausea OR (95% CI)	Memory problems OR (95% CI)	Anxiety OR (95% CI)	Depression OR (95% CI)	PCS (score ≤40) OR (95% CI)	MCS (score ≤40) OR (95% CI)
Treatment group Overall HSCT vs conventional therapy survivors*	0.8 (0.4-1.6)	1.2 (0.8-2.1)	0.8 (0.5-1.4)	0.7 (0.4-1.2)	1.0 (0.5-2.0)	0.8 (0.5-1.5)
Age at survey	1.0 (1.0-1.0)	1.0 (0.9-1.0)	1.0 (1.0-1.1)	1.1 (1.0-1.1)	1.1 (1.1-1.1)	1.1 (1.0-1.1)
Sex Female vs male*	1.9 (1.4-2.7)	1.5 (1.2-2.0)	1.3 (1.1-1.7)	1.3 (1.0-1.6)	1.5 (1.0-2.1)	1.5 (1.1-2.0)
Race/ethnicity White, non-Hispanic vs other*	1.1 (0.7-1.7)	1.8 (1.2-2.6)	1.1 (0.8-1.6)	0.9 (0.7-1.3)	1.0 (0.6-1.5)	1.1 (0.7-1.5)
Education <College vs ≥college*	1.4 (1.0-2.0)	2.1 (1.5-2.8)	1.3 (1.0-1.7)	1.5 (1.1-2.0)	2.6 (1.7-4.0)	2.1 (1.5-3.0)

*Reference group.

†CTCAE grades 3-4 vs none or 1-2.

Table 4. (continued)

Risk factors	Nausea OR (95% CI)	Memory problems OR (95% CI)	Anxiety OR (95% CI)	Depression OR (95% CI)	PCS (score ≤40) OR (95% CI)	MCS (score ≤40) OR (95% CI)
Marital status Single/divorced/other vs married/living with partner*	0.9 (0.6-1.3)	1.5 (1.1-2.0)	1.3 (1.0-1.7)	2.0 (1.5-2.6)	1.4 (0.9-2.0)	1.6 (1.2-2.2)
Cardiovascular†	1.2 (0.7-2.0)	0.9 (0.6-1.5)	1.1 (0.7-1.7)	1.6 (1.0-2.4)	2.8 (1.7-4.6)	1.6 (1.0-2.5)
Endocrine†	1.6 (1.1-2.3)	1.2 (0.9-1.6)	1.1 (0.9-1.4)	1.4 (1.1-1.9)	1.3 (0.9-1.9)	1.4 (1.0-1.8)
Gastrointestinal†	2.0 (1.2-3.1)	1.1 (0.7-1.7)	1.4 (1.0-2.1)	1.3 (0.9-1.9)	1.3 (0.8-2.1)	0.9 (0.6-1.4)
Neurology†	1.2 (0.6-2.2)	2.2 (1.4-3.5)	1.0 (0.6-1.6)	1.3 (0.8-2.1)	2.6 (1.6-4.4)	1.6 (1.0-2.6)
Ocular†	1.6 (0.6-4.2)	0.7 (0.3-1.7)	0.7 (0.3-1.6)	0.6 (0.2-1.5)	2.1 (0.8-5.4)	0.9 (0.3-2.2)
Pulmonary†	1.5 (0.8-2.7)	2.0 (1.2-3.3)	1.0 (0.6-1.7)	1.1 (0.6-1.9)	2.7 (1.6-4.8)	1.5 (0.9-2.6)
Reproductive†	1.5 (1.0-2.2)	1.1 (0.8-1.6)	1.1 (0.8-1.5)	1.2 (0.9-1.7)	1.3 (0.9-1.9)	0.9 (0.6-1.3)

*Reference group.

†CTCAE grades 3-4 vs none or 1-2.

of conventional therapy survivors (45.5%, 45.4%) were between 1980 and 1989 and between 1990 and 1999. The conventional therapy group had more survivors treated for acute lymphoblastic leukemia (58.7%) and lymphoma (37.3%), whereas the HSCT group had more survivors treated for acute myeloid leukemia (39.3%). Among 79 allogeneic HSCT survivors, 23 had a history of past chronic GVHD and 2 had active chronic GVHD at the time of evaluation. More HSCT survivors received alkylators, antimetabolites, dexamethasone, and total body irradiation (all $P < .05$), whereas more conventionally treated survivors received anthracyclines, high-dose methotrexate, prednisone, vincristine, and cranial/spinal radiation (all $P < .05$). For HSCT survivors, more participants had a shorter elapsed time since cancer diagnosis and history of second cancer compared with nonparticipants. For conventionally treated survivors, more participants were female, and had shorter elapsed time since diagnosis, history of second cancer and relapse, and received treatment with cranial radiation, but fewer received chest radiation, anthracyclines, antimetabolites, dexamethasone, and high-dose methotrexate compared with nonparticipants (all $P < .05$; supplemental Table 2).

Table 2 shows that the most prevalent symptom domains in HSCT and conventional therapy survivors, respectively, were pain (64.3%, 74.1%), sensation abnormalities (39.3%, 33.0%), anxiety (29.5%, 34.9%), and memory problems (28.6%, 25.0%). Approximately 64% of HSCT and 62% of conventionally treated survivors experienced symptoms in multiple domains. However, the prevalence of all symptom domains and poor PCS/MCS between survivors of HSCT and conventional therapy were not significantly different (all $P > .05$). Compared with noncancer controls, HSCT survivors had an elevated risk for abnormalities related to sensation (odds ratio [OR]: 4.7; 95% confidence interval [CI], 2.6-8.4), motor/movement (OR: 4.3; 95% CI, 1.6-11.0), cardiac (OR: 2.5; 95% CI, 1.1-5.6) and pulmonary symptoms (OR: 4.6; 95% CI, 1.8-11.8), fatigue (OR: 3.1; 95% CI, 1.4-7.0), memory problems (OR: 4.8; 95% CI, 2.5-9.2), anxiety (OR: 2.1; 95% CI, 1.2-3.6), and poor PCS (OR: 6.9; 95% CI, 2.8-17.0). Among 112 HSCT survivors, significant associations of having past or active chronic GVHD with symptom prevalence and poor HRQOL were only found in the sensation domain (OR: 4.2; 95% CI, 1.5-12.1), especially salient by the indication of having the symptom of very dry eyes (OR: 4.9; 95% CI, 1.8-13.3).

Table 3 shows that the risks of having cardiovascular, gastrointestinal, ocular, pulmonary, and reproductive CHCs among survivors treated with HSCT were significantly higher (all $P < .05$) than conventionally treated survivors and noncancer controls. Approximately, 47% of HSCT and 22% of conventional therapy survivors had multiple CHCs. Table 4 shows that the difference in prevalence of symptom domains and poor HRQOL between HSCT and conventionally treated survivors was not statistically significant (all $P > .05$) based on multivariable models. Longer time since cancer diagnosis was associated with a higher prevalence of some symptom domains (eg, sensation abnormalities, memory problems) and poor PCS for HSCT survivors vs conventionally treated survivors; however, the differences were not statistically significant (all $P > .05$) (supplemental Figure 2). In contrast, longer time since cancer diagnosis was associated with significantly higher prevalence of specific symptom items for survivors of HSCT vs conventional therapy, including double vision (OR: 2.8; $P = .04$), very dry eyes (OR: 3.4; $P < .0001$), and trouble seeing when wearing glasses (OR: 2.9; $P < .0001$) (supplemental Figure 3). Lower educational attainment and single/divorced marital status were significantly associated with elevated risks for motor/movement problems, pulmonary symptoms, memory problems, depression, and poor MCS (all $P < .05$).

The prevalence of abnormalities in symptom domains and HRQOL were significantly associated with the occurrence of specific CHCs (Table 4). Cardiovascular CHCs were associated with increased risks for cardiac symptoms (OR: 3.0; 95% CI, 1.8-4.9)

Table 5. Multivariable logistic regression for risks of symptom domain prevalence and poor HRQOL between overall HSCT survivors and noncancer controls by accounting for chronic health conditions

Risk factors	Sensation abnormalities OR (95% CI)	Motor/ movement problems OR (95% CI)	Cardiac symptoms OR (95% CI)	Pulmonary symptoms OR (95% CI)	Pain OR (95% CI)	Fatigue OR (95% CI)
Treatment group Overall HSCT survivors vs noncancer controls*	3.2 (1.5-6.8)	4.3 (1.2,15.4)	2.0 (0.7-5.7)	2.3 (0.6-8.0)	0.7 (0.3-1.4)	1.5 (0.5-4.7)
Age at survey	1.1 (1.0-1.1)	1.0 (1.0-1.1)	1.0 (1.0-1.1)	1.0 (1.0-1.1)	1.1 (1.0-1.1)	1.1 (1.0-1.1)
Sex Female vs male*	1.2 (0.7-2.1)	0.6 (0.2-1.5)	1.0 (0.4-2.2)	0.6 (0.2-1.6)	0.9 (0.6-1.5)	1.5 (0.7-3.3)
Race/ethnicity White, non-Hispanic vs other*	1.2 (0.6-2.4)	0.7 (0.2-2.3)	0.8 (0.3-2.2)	0.6 (0.2-1.5)	1.5 (0.8-2.8)	0.7 (0.3-1.8)
Education <College vs ≥college*	1.1 (0.6-1.9)	2.2 (0.8-6.4)	0.7 (0.3-1.7)	1.0 (0.4-2.5)	1.0 (0.6-1.6)	1.4 (0.6-3.1)
Marital status Single/divorced/other vs married/living with partner*	1.3 (0.7-2.4)	2.8 (0.9-8.7)	2.3 (0.9-5.8)	3.0 (1.0-8.7)	0.8 (0.5-1.5)	1.5 (0.6-3.6)
Cardiovascular†	1.5 (0.6-3.6)	1.8 (0.5-7.1)	4.9 (1.6,15.1)	0.9 (0.2-3.6)	2.4 (0.7-8.0)	3.4 (1.2-9.4)
Endocrine†	1.5 (0.8-2.7)	2.7 (1.0-7.3)	0.5 (0.2-1.4)	1.5 (0.6-4.1)	1.2 (0.7-2.1)	0.8 (0.3-2.0)
Gastrointestinal†	2.0 (0.9-4.2)	0.8 (0.2-3.1)	3.4 (1.3-9.0)	2.2 (0.7-6.5)	0.9 (0.4-2.0)	1.8 (0.7-4.9)
Neurology†	1.6 (0.6-4.3)	NA	0.3 (0.0-2.9)	0.4 (0.1-3.7)	3.9 (1.1-14.4)	0.7 (0.2-3.5)
Ocular†	2.2 (0.8-6.2)	1.9 (0.5-8.0)	1.2 (0.3-4.8)	1.0 (0.2-4.5)	4.5 (1.1-17.7)	1.1 (0.3-4.5)
Pulmonary†	1.4 (0.6-3.3)	0.4 (0.1-2.3)	3.6 (1.3-9.6)	5.3 (1.8,15.6)	1.5 (0.6-3.7)	2.1 (0.8-5.9)
Reproductive†	1.1 (0.6-2.3)	0.8 (0.2-2.5)	0.3 (0.1-1.0)	1.7 (0.6-5.1)	2.5 (1.1-5.6)	1.5 (0.6-4.0)

Risk factors	Nausea OR (95% CI)	Memory problems OR (95% CI)	Anxiety OR (95% CI)	Depression OR (95% CI)	PCS (score ≤40) OR (95% CI)	MCS (score ≤40) OR (95% CI)
Treatment group Overall HSCT survivors vs noncancer controls*	1.0 (0.4-2.6)	3.7 (1.5-8.9)	1.9 (0.9-3.9)	1.5 (0.7-3.3)	5.4 (1.6-18.6)	1.1 (0.5-2.6)
Age at survey	1.0 (0.9-1.0)	1.0 (1.0-1.1)	1.0 (1.0-1.0)	1.0 (1.0-1.1)	1.1 (1.0-1.2)	1.0 (1.0-1.1)
Sex Female vs male*	1.6 (0.8-3.3)	0.9 (0.4-1.7)	1.3 (0.8-2.3)	0.9 (0.5-1.6)	1.3 (0.5-3.1)	1.4 (0.8-2.7)
Race/ethnicity White, non-Hispanic vs other*	1.0 (0.4-2.4)	0.9 (0.4-2.2)	0.9 (0.5-1.7)	0.7 (0.4-1.4)	2.5 (0.6-9.6)	1.5 (0.6-3.4)
Education <College vs ≥college*	1.4 (0.7-3.0)	2.5 (1.1-5.3)	1.5 (0.9-2.7)	1.5 (0.8-2.7)	2.2 (0.9-5.5)	1.8 (1.0-3.5)

*Reference group.

†CTCAE grades 3-4 vs none or 1-2.

Table 5. (continued)

Risk factors	Nausea OR (95% CI)	Memory problems OR (95% CI)	Anxiety OR (95% CI)	Depression OR (95% CI)	PCS (score ≤40) OR (95% CI)	MCS (score ≤40) OR (95% CI)
Marital status Single/divorced/other vs married/living with partner*	1.2 (0.5-2.5)	3.7 (1.6-8.4)	1.2 (0.6-2.3)	2.2 (1.1-4.2)	2.5 (0.9-6.5)	1.6 (0.8-3.2)
Cardiovascular†	1.2 (0.4-3.9)	1.0 (0.3-3.0)	0.8 (0.3-2.1)	0.8 (0.3-2.2)	2.8 (0.9-8.1)	0.9 (0.3-3.0)
Endocrine†	1.2 (0.6-2.4)	0.6 (0.2-1.3)	1.1 (0.6-1.9)	2.2 (1.2-4.0)	3.2 (1.3-8.0)	1.4 (0.7-2.7)
Gastrointestinal†	3.2 (1.4-7.5)	3.5 (1.5-8.3)	2.8 (1.3-5.8)	1.2 (0.5-2.8)	2.5 (0.9-6.5)	1.4 (0.6-3.4)
Neurology†	0.6 (0.1-2.8)	2.4 (0.8-7.6)	1.4 (0.5-3.8)	1.0 (0.3-2.8)	3.3 (1.0-11.2)	1.6 (0.6-4.5)
Ocular†	1.0 (0.2-3.9)	0.5 (0.2-1.8)	0.7 (0.2-2.0)	0.5 (0.1-1.8)	1.6 (0.4-6.1)	0.4 (0.1-1.9)
Pulmonary†	1.1 (0.4-3.3)	1.9 (0.7-4.8)	2.0 (0.9-4.5)	2.3 (1.0-5.5)	1.3 (0.4-4.1)	1.8 (0.7-4.7)
Reproductive†	1.2 (0.5-3.2)	1.5 (0.6-3.5)	1.1 (0.5-2.2)	1.2 (0.6-2.7)	0.9 (0.3-2.3)	1.8 (0.8-4.2)

*Reference group.

†CTCAE grades 3-4 vs none or 1-2.

and poor PCS (OR: 2.8; 95% CI, 1.7-4.6). Pulmonary CHCs were associated with a higher risk for pulmonary symptoms (OR: 2.5; 95% CI, 1.4-4.3), cardiac symptoms (OR: 3.0; 95% CI, 1.7-5.3), and poor PCS (OR: 2.7; 95% CI, 1.6-4.8). Neurological CHCs were associated with a higher risk for motor/movement problems (OR: 3.3; 95% CI, 2.0-5.5), memory problems (OR: 2.2; 95% CI, 1.4-3.5), and poor PCS (OR: 2.6; 95% CI, 1.6-4.4). After adding specific cancer therapy (chemotherapy agents, total body irradiation, and other radiation exposures) as covariates to the parsimonious models focusing on HSCT status (ie, receipt of HSCT vs conventional therapy) and CHCs, the occurrence of organ-specific CHCs was still significantly associated with poor patient-reported outcomes with similar magnitudes (all $P < .05$), whereas HSCT status and cancer therapy were not (all $P > .05$; supplemental Table 3).

Table 5 shows that HSCT recipients, compared with noncancer controls, were at elevated risks for abnormalities related to sensation (OR: 3.2; 95% CI, 1.5-6.8), motor/movement (OR: 4.3; 95% CI, 1.2-15.4), memory (OR: 3.7; 95% CI, 1.5-8.9) symptoms, and poor PCS (OR: 5.4; 95% CI, 1.6-18.6). Cardiovascular CHCs were associated with increased risks for cardiac symptoms (OR: 4.9; 95% CI, 1.6-15.1) and fatigue (OR: 3.4; 95% CI, 1.2-9.4). Pulmonary CHCs were associated with a higher risk for pulmonary (OR: 5.3; 95% CI, 1.8-15.6) and cardiac symptoms (OR: 3.6; 95% CI, 1.3-9.6).

Supplemental Tables 4 and 5 show that the type of HSCT received (allogeneic vs autologous) and most of the transplant-specific factors were not significantly associated with symptoms prevalence or poor HRQOL (all $P > .05$). Relapse/progression of hematologic malignancy was the only transplant factor significantly associated with a higher risk of more motor/movement problems (OR: 17.5; 95% CI, 2.2-138.2).

Discussion

In this large clinically assessed pediatric cancer survivor cohort, pain, sensation abnormalities, anxiety, and memory problems were the most prevalent symptom domains (>25%) endorsed by survivors treated with HSCT. However, the prevalence of impaired symptom domains and poor HRQOL in survivors treated with HSCT was similar to those treated with conventional therapy, but significantly higher than noncancer controls. The occurrence of organ-specific CHCs, rather than HSCT or transplant-related variables, were significant predictors of organ-related symptoms and poor HRQOL (eg, cardiovascular CHCs for cardiac symptoms; neurological CHCs for motor/movement symptoms). Additionally, socioeconomic vulnerability (eg, lower educational attainment, single/divorced marital status) explained variation in patient-reported outcomes.

As anticipated, HSCT survivors exhibited an excess prevalence of symptoms and impairment in HRQOL compared with noncancer controls, but surprisingly there was no difference in these outcomes between HSCT and conventionally treated survivors. This finding could be explained by several factors. First, the lack of difference is likely related to the relatively low prevalence of chronic GVHD experience (N = 25; 22.3%) in our HSCT group, which reflects a conservative approach in donor selection during the early years of our transplant program. Additionally, chronic GVHD in 23 HSCT survivors had been resolved at the time of assessment. A previous study found that although active chronic GVHD was significantly associated with severe adverse events in adult survivors of childhood cancer, health status in survivors with resolved chronic GVHD was equivalent to those who had never been diagnosed with GVHD.[8] Second, patients surviving life-threatening conditions may adapt to disadvantaged circumstances, a phenomenon known as response shift.[32,33] Evidence suggests that childhood HSCT survivors might

change their conceptualizations and thresholds for the presence or severity of patient-reported outcomes over time.[34,35] Third, HSCT recipients have lower survival rates[36] or may have been too ill to enroll in this study because of transplant-related complications or higher prevalence of severe/disabling health status as compared with conventionally treated survivors.[7,8,37] Therefore, the true prevalence of patient-reported outcome impairment in HSCT survivors might be underestimated.

We found that having a history of past or active chronic GVHD was significantly associated with higher prevalence of sensation symptom domain (especially the symptom of very dry eyes), and receiving HSCT was significantly associated with higher cumulative prevalence of ocular symptoms (double vision, very dry eyes, and trouble seeing when wearing glasses), which were part of sensation domain. The underlying clinical causes are likely multifactorial. Ocular manifestations appear in 60% to 90% of patients with GVHD.[38] Additionally, specific HSCT complications, including keratoconjunctivitis sicca, pseudomembranous conjunctivitis, corneal ulceration, and microvascular retinopathy, may contribute to the development of ocular symptoms.[38]

Virtually all adult survivors of childhood cancers develop at least 1 CHC, and the risk increases with the duration of time since therapy completion.[27,39] In comparison with conventionally treated survivors, those treated with HSCT experience elevated risks for infections,[9] dyslipidemia, lung disease, cataracts, osteonecrosis, and secondary malignancies.[7] By accounting for the influence of CHCs, we found that prevalence of symptom domains was highly associated with CHCs from the same organ system (eg, cardiac), and the magnitude for associations of both symptom prevalence and poor HRQOL with HSCT status (eg, HSCT vs conventional therapy or noncancer) decreased. Specifically, excessive prevalence of pulmonary symptoms, anxiety, and fatigue was explained by the occurrence of specific CHCs rather than transplant per se, which suggests that the development of various CHCs following transplant underlies the pathway of poor patient-reported outcomes. Because symptom presence is a manifestation of CHCs, focusing on symptoms as early indicators of adverse health conditions is clinically relevant. Interestingly, undergoing a HSCT, rather than the occurrence of CHCs, was significantly associated with the prevalence of neuropsychological/cognitive symptoms (ie, sensation abnormalities, motor/movement problems, and memory problems). This finding indicates the failure to appreciate the importance of integrating patient-reported outcomes into evaluating morbidities during survivorship care.[28]

Although childhood cancer survivors develop multiple symptoms,[12] the mechanisms behind cooccurring multiple symptoms in childhood cancer survivors remain understudied. Underlying biophysiological mechanisms (eg, endothelial dysfunction or systemic inflammation related to treatment exposures[40-42]) may contribute to the concurrent symptoms. Experience with chronic GVHD, a systemic inflammatory response by donors' immune systems, resulting in multisystem organ damage in the host, may also lead to cooccurring multiple symptoms in survivors treated with HSCT and further affect HRQOL.[10,21,43,44] Pain syndromes in cancer survivors related to the exposure to neurotoxic chemotherapeutic agents or ionizing radiation have been reported several years after completion of therapy.[45] Both chronic pain and chronic GVHD have been associated with depressive symptoms in adult cancer survivors treated with HSCT.[10,46]

Although we identified disadvantaged sociodemographic status (eg, less than college education) as risk factors of symptom prevalence and poor HRQOL, other psychosocial factors not available in this study (eg, coping behaviors, cognitive appraisal, family support) may have influenced the development of psychological symptoms in cancer survivors.[18,47]

The goal of cancer survivorship care is not merely to identify and manage medical complications, but also to improve daily functional status and HRQOL. The findings of high symptom prevalence in several domains and poor HRQOL for adult survivors of childhood hematologic malignancies highlight the usefulness of implementing comprehensive symptom screening regularly to identify potential adverse health events and facilitate timely referral for early interventions, especially for HSCT survivors who have a substantial burden of CHCs. Strategies to improve HSCT survivorship care by developing a standardized symptom screening tool, using relevant symptom domains for evaluation, and determining a meaningful screening period are warranted.

Several limitations should be noted. First, our sample was recruited from adult survivors of childhood hematologic malignancies who were treated at a single institution. Our results may not be generalizable to other survivor populations. Second, we included a relatively small number of survivors treated with HSCT in the analyses. Although our study population represents 1 of the largest groups of long-term HSCT survivors with systematically clinically assessed outcomes, the overall size of the study sample does limit statistical power. Future clinical investigation of HSCT survivors will be important to validate and expand upon our findings. Third, the inclusion of survivors with heterogeneous cancer diagnoses may confound the comparison of patient-reported outcomes in HSCT and conventional therapy survivors. However, the adjustment of comprehensive treatment variables in our analyses addresses this concern. Fourth, because of the nature of cross-sectional study design, the causal relationship between symptom prevalence and CHC occurrence is unknown. Future longitudinal research is warranted to answer this question. Last, our symptom measures merely capture the attribute of symptom presence rather than frequency or severity. Future studies are needed to replicate our design by using comprehensive tools (eg, the Patient-Reported Outcomes version of the CTCAE[48] with additional HSCT-specific items) to improve the accuracy and clinical relevance for symptom assessment.

In conclusion, poor patient-reported outcomes including symptom prevalence and poor HRQOL are concerning issues in survivors of childhood hematologic malignancies, whether treated with conventional therapy or HSCT. Symptom prevalence and poor HRQOL were more closely related to the occurrence of CHCs than the mode of therapy, at least among the heterogeneous group of survivors featured in this report. Routine screening of symptom phenotypes may help identify adverse health events in adult survivors of childhood hematologic malignancies, especially for survivors treated with HSCT who have a substantial burden of CHCs.

Acknowledgments

Research reported in this publication was supported by the National Institutes of Health, National Cancer Institute (U01CA195547, R01CA238368, and P30CA021765-33). The content is solely the

responsibility of the authors and does not necessarily represent the official views of the funding agency.

Authorship

Contribution: H.-J.Y. and I.-C.H. undertook concept and design; L.L.R. and M.M.H. provided study materials; M.J.E., N.B., K.K.N., K.R.K., L.L.R., M.M.H., and I.-C.H. collected and assembled data; H.M.E., N.S.B., S.H., M.J.E., N.B., D.K.S., L.L.R., M.M.H., and I.-C.H. undertook data analysis and clinical interpretation; H.-J.Y. and I.-C.H. wrote the manuscript; and all authors edited the article and provided final approval.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: H.-J.Y., 0000-0001-9606-7354; M.J.E., 0000-0003-2781-9983; K.K.N., 0000-0002-2084-1507; L.L.R., 0000-0001-7460-8578; M.M.H., 0000-0001-6984-2407; I.-C.H., 0000-0002-1194-3923.

Correspondence: I-Chan Huang, Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, MS-735, 262 Danny Thomas Pl, Memphis, TN 38105; e-mail: i-chan.huang@stjude.org.

Footnotes

Submitted 23 October 2019; accepted 5 March 2020; prepublished online on *Blood* First Edition 2 April 2020. DOI 10.1182/blood.2019003858.

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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