Original Article

Neurocognitive, Psychosocial, and Quality-of-Life Outcomes in Adult Survivors of Childhood Non-Hodgkin Lymphoma

Matthew J. Ehrhardt, MD, MS[1,2]; Daniel A. Mulrooney, MD, MS[1,2]; Chenghong Li, PhD[3]; Malek J. Baassiri, MD[1,4]; Kari Bjornard, MD, MPH[1]; John T. Sandlund, MD[1]; Tara M. Brinkman, PhD[2,5]; I-Chan Huang, PhD[2]; Deo Kumar Srivastava, PhD[3]; Kirsten K. Ness, PhD[2]; Leslie L. Robison, PhD[2]; Melissa M. Hudson, MD[1,2]; and Kevin R. Krull, PhD[2,5]

BACKGROUND: Children with non-Hodgkin lymphoma (NHL) undergo treatment with central nervous system–directed therapy, the potentially neurotoxic effects of which have not been reported in NHL survivors. **METHODS:** NHL survivors (n = 187) participating in the St. Jude Lifetime Cohort who were 10 or more years from their diagnosis and were 18 years old or older underwent neurocognitive, emotional distress (Brief Symptom Inventory 18), and health-related quality of life (HRQOL) assessments (36-Item Short Form Health Survey). Age-adjusted *z* scores were compared with community controls (n = 181) and normative data. Treatment exposures were abstracted from medical records. Models adjusted for the age, sex, and time from diagnosis were used to calculate the risk of impairment. **RESULTS:** The mean ages at evaluation were similar for the survivors and the controls (35.7 ± 8.9 vs 35.5 ± 11.0 years; $P = .86$). Survivors were 25.2 ± 8.8 years from their diagnosis: 43 (23%) received cranial radiation, 70 (37%) received high-dose methotrexate, 40 (21%) received high-dose cytarabine, and 151 (81%) received intrathecal chemotherapy. Survivors' intelligence and attention were within normal limits; however, their memory, executive function, processing speed, and academics were impaired in comparison with both population norms and community controls (*P* values < .05). Treatment-related exposures were not associated with neurocognitive function; however, neurocognitive impairment was associated with lower educational attainment, unemployment, and occupational status (*P* values < .03). Slower processing speed and worse self-reported executive function were associated with symptoms of depression (*P* values ≤ .003) and poorer HRQOL (*P* values < .05). **CONCLUSIONS:** Adult survivors of childhood NHL experience impaired neurocognitive function, which is associated with lower social attainment and poor HRQOL. Early-detection and intervention strategies are recommended. ***Cancer* 2018;124:417-25.** © *2017 American Cancer Society.*

KEYWORDS: cognitive function, health-related quality of life, lymphoma, non-Hodgkin lymphoma, survivorship.

INTRODUCTION

Treatment for childhood cancer has advanced such that more than 80% of newly diagnosed children are expected to become long-term survivors.[1] Improved survival has led to the recognition of many potential late effects of therapy, including impaired neurocognitive function, mental health, and health-related quality of life (HRQOL).[2,3]

Trends in childhood non-Hodgkin lymphoma (NHL) survival rates have mirrored those of the larger population of children with cancer. Similarly to other survivors, many NHL survivors have received central nervous system (CNS)–directed chemotherapy and/or cranial radiation therapy (CRT), which have been shown to negatively affect late neurocognitive function,[4] in addition to non–CNS-directed radiation,[5] which is associated with neurocognitive impairment in Hodgkin lymphoma survivors.[6] Despite exposures to similar agents, the cumulative doses, frequencies, and durations of treatment inherent to NHL regimens may have unique adverse effects; however, few studies have assessed the impact of these agents on neurocognitive and social outcomes in NHL survivors.[7-10] No studies have specifically addressed the potential impacts of neurocognitive deficits on social outcomes, emotional functioning, and HRQOL.

In an effort to balance neurotoxic exposures with adequate CNS disease control, frontline NHL treatment strategies have replaced CRT with CNS-directed systemic and intrathecal chemotherapy.[11] For example, a similar strategy has reduced but not eliminated the neurocognitive sequelae experienced by acute lymphoblastic leukemia (ALL) survivors[12];

Corresponding author: Matthew J. Ehrhardt, MD, MS, Division of Cancer Survivorship, Department of Oncology, St. Jude Children's Research Hospital, 262 Danny Thomas Place, MS 735, Memphis, TN 38105; matthew.ehrhardt@stjude.org

[1]Department of Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee; [2]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, Tennessee; [3]Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, Tennessee; [4]Department of Oncology, Hammoud Hospital University Medical Center, Saida, Lebanon; [5]Department of Psychology, St. Jude Children's Research Hospital, Memphis, Tennessee

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Additional supporting information may be found in the online version of this article

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however, because of the unique cumulative doses, frequencies, and durations of exposures relevant to NHL therapies, the impact of similar modifications in NHL survivors remains unknown. An understanding of late neurotoxicities in cohorts treated with either historical or contemporary NHL protocols is needed to facilitate surveillance and anticipatory guidance for both aging and newly emerging survivors. Our objective was to identify the risk for neurocognitive deficits and their subsequent effects on social outcomes, emotional functioning, and HRQOL in adult survivors of childhood NHL.

MATERIALS AND METHODS

Study Design

We performed a retrospective cohort analysis among participants enrolled in the St. Jude Lifetime Cohort Study (SJLIFE). The methods for this institutional review board–approved study have been described previously.[13]

Participants

This analysis included survivors treated for childhood NHL at St. Jude Children's Research Hospital who were 18 years old or older and had survived 10 or more years after their diagnosis. In agreement with the established SJLIFE methodology, medical events and cumulative treatment exposures were abstracted from survivor health records (medical reports, cancer registry follow-up, and/or contact with the next of kin for deceased individuals or those lost to follow-up) by clinical research associates trained in medical record abstraction. Quality assurance was provided through a routine review of exposures for clinical accuracy.[13] Individuals who were non–English-speaking, had genetic/preexisting neurodevelopmental disorders associated with neurocognitive impairment, and/or incurred injury resulting in neurocognitive impairment unrelated to their cancer therapy (eg, traumatic brain injury) were excluded from the neurocognitive evaluation. Control subjects were recruited from acquaintances of St. Jude patients, survivors, and employees in an effort to establish a comparison population with similar baseline characteristics.

Study Procedures

The core evaluation included a physical examination, a comprehensive laboratory assessment, objective neurocognitive testing, and questionnaires detailing the demographics, medical history, neurobehavioral symptoms, emotional distress, HRQOL, and health habits. Risk-based screening evaluations were performed according to the Children's Oncology Group guidelines.[14] For this study, only cardiac (cardiomyopathy, hypertension, and hypercholesterolemia) and endocrine conditions (primary hypothyroidism, elevated fasting glucose, and overweight/obesity) were graded (with a modified late-effect grading scale)[15] because of their high prevalence in NHL survivors[5] and their association with neurocognitive impairment in the general population.[16-18]

Outcomes

The primary outcome was neurocognitive performance. Evaluations were performed by certified examiners and supervised by a board-certified neuropsychologist. Objective neurocognitive performance and patient-reported outcomes (PROs) were assessed with the instruments listed in Supporting Table 1 (see online supporting information).

Social outcomes were determined from patient-reported questionnaires. The level of education (less than a college degree vs a college degree or more), employment status (unemployment vs partial or full-time employment, home care provider, students), occupation status (service/blue collar vs professional/managerial), living status (dependent [with a parent] vs independent [with a spouse, roommates, or siblings or alone]), annual income ($<\$40{,}000$ vs $\geq \$40{,}000$), and marital status (never married vs ever married) were determined. The occupation (service/blue collar vs professional/managerial) was classified according to previously reported methods, which accounted for updated categories defined by the US Bureau of Labor Statistics.[8,19]

Statistical Analysis

Summary statistics were generated, and 1- and 2-sample t tests were performed to compare mean age-adjusted z scores for the outcomes of interest with both normative data and community controls, respectively. We chose a conservative approach in which only outcomes for which survivor performance differed significantly from both normative data and community controls were considered clinically relevant and carried forward for analyses. Dual comparisons were performed to strengthen our results: 1) they maximized the likelihood that detectable differences were truly significant, and 2) they ensured a uniformly tested (across all outcomes) comparison cohort (community controls) while still considering normative data. Comparisons between survivors and community controls were adjusted for background differences in sex. The false-discovery rate methodology was used to correct P values for multiple comparisons.[20] A threshold of $P < .05$ with false-discovery rate correction was used.

For the identified outcomes, multivariate linear regression was conducted to examine the effects of CRT,

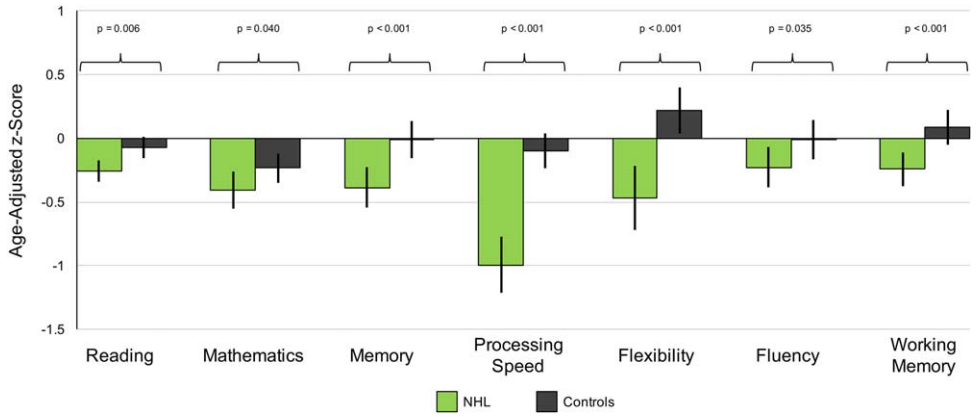

Figure 1. Neurocognitive performance in NHL survivors versus community controls. NHL indicates non-Hodgkin lymphoma.

chemotherapy, and chronic conditions, with adjustments made for patient characteristics such as illicit drug use and emotional distress. Because of potential confounding, chemotherapy agents were analyzed in the subgroup of patients who did not receive CRT. For multivariate models, *P* values were not adjusted for multiple comparisons because such models were based on a priori decisions.

Modified Poisson regression analyses were performed to associate impaired neurocognitive outcomes with education and employment, with adjustments made for demographics. Among employed survivors, the effect of neurocognitive function on occupation was explored. Multiple linear regression analyses, adjusted for demographics, were performed to examine the effects of neurocognitive function on HRQOL. All statistical tests were 2-sided and were performed with SAS 9.3.

RESULTS

Of 315 eligible SJLIFE survivors, 187 (59.4%) underwent neurocognitive testing (Supporting Fig. 1 [see online supporting information]). Participating survivors had a median age of 10.4 years (range, 1.8-20.8 years) at diagnosis and were a median of 25.5 years (range,10.5-47.7 years) from their diagnosis. Participants were more likely than nonparticipants to be female, but they did not differ by race or treatment-related exposures (Supporting Table 2 [see online supporting information]). The age at evaluation did not differ between survivors (35.1 years) and community controls (34.4 years; $P = .86$). Sex differed between survivors, who were 35% female, and community controls, who were 52% female ($P < .01$), and thus was used as a covariate in subsequent analyses. Participants were previously treated with CRT (23%), high-dose methotrexate (37%), high-dose cytarabine (21%), anthracyclines (79%), and intrathecal chemotherapy (81%). Histological lymphoma subtypes included the following: mature B cell in 111 (59%), lymphoblastic in 63 (34%), anaplastic large cell in 5 (3%), and other or unspecified in 8 (4%).

Comparisons of survivor, community control, and normative data for neurocognitive performance and PROs for neurobehavioral and emotional outcomes are presented in Supporting Table 3 (see online supporting information). Survivors demonstrated worse academics (reading and mathematics), visual learning and working memory, motor processing speed, cognitive flexibility, and cognitive fluency in comparison with community controls (*P* values $\leq .04$) and population-normative data (*P* values $\leq .01$; Fig. 1). Survivors reported worse shifting, emotional control, working memory, anxiety, depression, and somatization in comparison with community controls (*P* values $\leq .04$) and population-normative data (*P* values $\leq .005$). For nearly all outcomes that differed significantly from community controls and normative data, >20% to 30% of survivors scored in the lowest 10th percentile (>1.3 standard deviations below the mean) of the general population (Supporting Table 3).

A trend toward lower neurocognitive performance was observed in survivors with moderate to severe chronic conditions in comparison with those with no or mild chronic conditions (Fig. 2). In adjusted models, higher grade conditions were not associated with neurocognitive performance (Table 1). In separate adjusted models, CRT, high-dose methotrexate, and/or high-dose cytarabine, anthracyclines, and intrathecal chemotherapy were not associated with neurocognitive performance. Males demonstrated significantly lower processing speed than females across all adjusted models. Higher emotional distress was associated with poorer processing speed, executive function, and PRO executive function (Table 1).

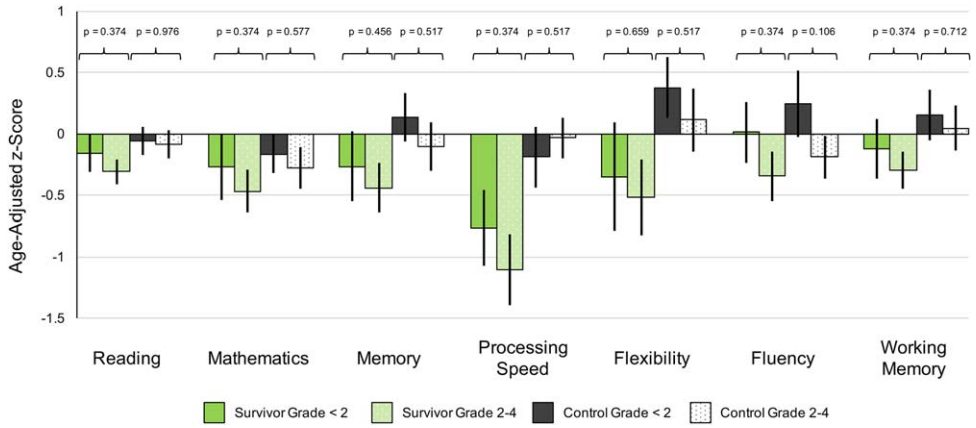

Figure 2. Neurocognitive performance in non-Hodgkin lymphoma survivors by the severity of chronic conditions.

TABLE 1. Risk Factors Associated With Impaired Neurocognitive Performance in Non-Hodgkin Lymphoma Survivors

	Academics[a]		Memory		Processing Speed		Executive Function[b]		PRO Executive Function[c]	
	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*
Overall cohort										
Model 1a (chronic conditions)										
Male sex	0.03	.759	0.28	.105	**−0.71**	**.002**	−0.08	.591	−0.21	.242
Grade 2-4 chronic condition (vs grade 0 or 1)	−0.23	.054	−0.17	.364	−0.44	.077	−0.27	.092	0.26	.184
Model 1b (psychological)										
Male sex	−0.02	.838	0.25	.170	**−0.66**	**.002**	−0.10	.511	−0.08	.574
Illicit drug use (yes/no)[d]	0.03	.763	0.16	.368	−0.16	.447	0.07	.658	0.23	.092
Psychoactive medication use (yes/no)[e]	−0.03	.884	0.30	.354	0.001	.998	−0.14	.625	0.28	.299
Somatization (per SD)[f]	**−0.17**	**.011**	−0.10	.358	−0.20	.110	**−0.21**	**.015**	**0.35**	**<.001**
Depression (per SD)[f]	−0.05	.436	0.04	.652	**−0.35**	**.003**	−0.04	.657	**0.40**	**<.001**
Model 1c (cranial radiation)										
Male sex	0.03	.760	0.26	.121	**−0.71**	**.002**	−0.08	.574	−0.20	.250
Cranial radiation (yes/no)	−0.11	.418	−0.28	.179	−0.06	.821	−0.20	.262	0.20	.351
Cohort with no cranial radiation										
Model 2 (chemotherapy)										
Male sex	−0.02	.871	0.26	.176	**−0.82**	**.002**	−0.02	.931	−0.10	.638
High-dose MTX or ARAC (yes/no)	−0.04	.799	0.07	.775	0.05	.868	−0.04	.858	0.09	.708
Anthracycline (10 mg/m^2)	0.001	.898	0.01	.118	0.01	.607	0.001	.897	0.02	.096
Intrathecal chemotherapy										
Single- or double-agent	0.15	.436	−0.30	.289	0.08	.833	0.12	.640	−0.37	.233
Triple-agent	0.03	.881	−0.37	.249	−0.01	.979	0.14	.647	−0.45	.217

Abbreviations: ARAC, cytarabine; MTX, methotrexate; PRO, patient-reported outcome; SD, standard deviation.
All models were adjusted for the age at diagnosis and the time from diagnosis. Bolding indicates *P* values < .05. Neurocognitive functions for which survivors differed significantly from community controls and population-normative data are shown. Estimates are presented in standardized units and reflect values of change in *z*-score units (mean, 0; SD, 1.0). Scores less than 0 reflect a poor performance for neurocognitive testing (reading, memory, processing speed, and executive function). Scores greater than 0 reflect more symptoms of impairment for PRO executive function.
[a] Average of reading and mathematics scores.
[b] Average of cognitive flexibility, fluency, and working memory scores.
[c] Average of emotional control, shifting, and working memory scores.
[d] Any lifetime marijuana, cocaine, and/or amphetamine use.
[e] Current antidepressant, anxiolytic/sedative/hypnotic, opioid, stimulant, neuroleptic, and/or anticonvulsant use.
[f] Brief Symptom Inventory score (per SD).

Survivors demonstrated poorer social outcomes than community controls (Supporting Table 4 [see online supporting information]). Neurocognitive function and PRO neurobehavioral symptoms were associated with a number of these outcomes (Table 2). After adjustments for the age at diagnosis, time from diagnosis, and sex, survivors with lower academic function (relative risk [RR], 1.59; 95% confidence interval [CI], 1.25-2.03; $P < .001$)

TABLE 2. Associations Between Neurocognitive Performance and Social Attainment

Neurocognitive Predictors[a]	Less Than College Degree			Unemployed			Service/Blue-Collar Employment		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Academics[b]	**1.59**	**1.25-2.03**	**<.001**	1.24	0.75-2.06	.398	0.97	0.74-1.28	.853
Memory	0.97	0.87-1.08	.569	1.07	0.79-1.45	.660	1.07	0.93-1.23	.331
Processing speed	0.99	0.91-1.08	.805	**1.25**	**1.03-1.52**	**.025**	0.91	0.80-1.04	.182
Executive function[c]	1.14	0.97-1.35	.123	1.34	0.80-2.23	.267	**1.73**	**1.36-2.21**	**<.001**
PRO executive function[d]	0.98	0.89-1.08	.685	1.11	0.87-1.42	.388	**1.15**	**1.02-1.31**	**.027**

Neurocognitive Predictors[a]	Dependent Living			<$40,000/y Income			Never Married		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Academics[b]	**0.49**	**0.26-0.94**	**.032**	1.05	0.78-1.43	.735	0.70	0.42-1.16	.166
Memory	**1.50**	**1.12-2.01**	**.006**	1.01	0.86-1.18	.919	1.12	0.89-1.41	.336
Processing speed	1.24	1.00-1.54	.051	0.98	0.85-1.12	.742	1.10	0.90-1.34	.349
Executive function[c]	**2.13**	**1.40-3.23**	**<.001**	1.28	0.97-1.69	.077	1.07	0.73-1.57	.732
PRO executive function[d]	1.10	0.89-1.37	.380	1.14	0.98-1.32	.086	0.94	0.74-1.18	.575

Psychological Predictors	Less Than College Degree			Unemployed			Service/Blue-Collar Employment		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Illicit drug use (yes/no)[e]	**1.37**	**1.06-1.78**	**.017**	0.98	0.54-1.78	.952	1.34	1.00-1.80	.050
Somatization (per SD)[f]	1.05	0.92-1.20	.450	1.16	0.84-1.61	.366	1.15	1.00-1.32	.051
Depression (per SD)[f]	1.02	0.90-1.15	.802	**1.85**	**1.45-2.37**	**<.001**	1.05	0.91-1.22	.499

Psychological Predictors	Dependent Living			<$40,000/y Income			Never Married		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Illicit drug use (yes/no)[e]	0.84	0.48-1.49	.553	0.89	0.64-1.23	.472	0.69	0.44-1.08	.103
Somatization (per SD)[f]	1.23	0.87-1.75	.245	0.86	0.71-1.06	.153	0.86	0.66-1.11	.246
Depression (per SD)[f]	1.36	0.99-1.87	.060	**1.55**	**1.32-1.83**	**<.001**	**1.44**	**1.19-1.73**	**<.001**

Abbreviations: CI, confidence interval; PRO, patient-reported outcome; RR, relative risk; SD, standard deviation.
All models were adjusted for the age at diagnosis, time from diagnosis, and sex. Bolding indicates *P* values < .05. Neurocognitive functions for which survivors differed significantly from community controls and population-normative data are shown. Social attainment was determined from patient-reported questionnaires (see the Materials and Methods section).
[a] Impaired neurocognitive function was defined as scores falling within the worst 10th percentile for the general population.
[b] Average of reading and mathematics scores.
[c] Average of cognitive flexibility, fluency, and working memory scores.
[d] Average of emotional control, shifting, and working memory scores.
[e] Any lifetime marijuana, cocaine, and/or amphetamine use.
[f] Brief Symptom Inventory score (per SD worse than population-normative data).

were more likely to not graduate from college. Survivors with impaired memory (RR, 1.5; 95% CI, 1.12-2.01; $P = .006$) and executive function (RR, 2.13; 95% CI, 1.40-3.23; $P < .001$) were more likely to live dependently. Those with slower processing speed (RR, 1.25; 95% CI, 1.03-1.52; $P = .025$) were more likely to be unemployed. Among employed survivors (excluding home care providers and students), those with impaired executive function (RR, 1.73; 95% CI, 1.36-2.21; $P < .001$) and PRO executive function (RR, 1.15; 95% CI, 1.02-1.31; $P = .027$) were more likely to hold service/blue-collar occupations. Survivors who reported illicit drug use were more likely to not graduate from college (RR, 1.37; 95% CI, 1.06-1.78; $P = .017$), whereas those with self-reported symptoms of depression were more likely to be unemployed (RR, 1.85; 95% CI, 1.45-2.37; $P < .001$), to earn < $40,000/y (RR, 1.55; 95% CI, 1.32-1.83; $P < .001$), and to have never been married (RR, 1.44; 95% CI, 1.19-1.73; $P < .001$).

Survivors reported worse bodily pain, general health, vitality, social functioning, role limitations due to emotional health problems, and mental health in comparison with community controls (*P* values ≤ .005) and population-normative data (*P* values < .05; Fig. 3 and Supporting Table 3 [see online supporting information]). Models, adjusted for the age at diagnosis, time from diagnosis, sex, and those neurocognitive outcomes that differed from both community controls and normative data,

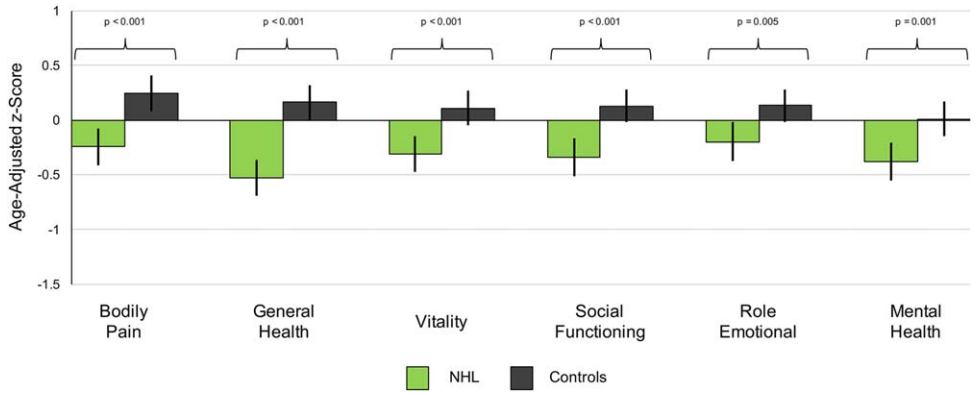

Figure 3. Quality of life in NHL survivors versus controls. NHL indicates non-Hodgkin lymphoma.

are presented in Supporting Table 5 (see online supporting information). Survivors with slower processing speed reported worse role emotional ($P < .001$), general ($P = .017$), and mental health ($P = .022$), whereas survivors who reported worse PRO executive function also reported worse bodily pain, general health, vitality, social functioning, role emotional health, and mental health (P values $< .001$).

DISCUSSION

We report novel neurocognitive, psychosocial, and quality-of-life outcomes for the largest cohort of adult survivors of childhood NHL to date. For the majority of the outcomes in which survivors differed from both community controls and normative data, 2 to 3 times as many survivors demonstrated impairment as would be expected in the general population, and this underscores the importance of better characterizing the specific challenges faced by this previously understudied group. NHL survivors demonstrated impaired neurocognitive function unrelated to cancer treatment; however, lower neurocognitive performance was associated with worse social outcomes and HRQOL.

Many have reported associations between cancer treatments and neurocognitive impairment in ALL survivors.[12,21-23] Similar studies have not been performed with NHL survivors despite the use of similar potentially neurotoxic treatment agents, and opportunities to inform screening and early interventions have possibly been missed. In contrast to the existing literature on ALL survivors, we did not identify associations between treatment-related exposures and neurocognitive outcomes in NHL survivors; this possibly reflects differences in the dose intensity and frequency between ALL and NHL protocols as well as the older diagnostic age of NHL patients. We found strong associations between emotional distress and neurocognitive problems. Survivors diagnosed during adolescence and young adulthood may be more prone to emotional distress because the cancer experience occurs during a key phase of psychosocial development.[24] Because many cases of childhood NHL occur during adolescence, interventions targeting emotional distress may help to mitigate long-term neurocognitive sequelae in these survivors.

NHL survivors experienced significantly reduced processing speed in comparison with both community controls and normative data. One-third of survivors scored within the lowest 10th percentile of normative data for motor processing. More specifically, we identified reduced processing speed in male NHL survivors, and this was independent of treatment exposures and the presence of chronic health conditions. Because of the predilection for childhood NHL in males, many newly diagnosed individuals may continue to experience processing speed deficits. This is concerning because reduced processing speed was associated with unemployment and worse role emotional, general, and mental health. Future investigations into the timing of the onset and trajectory of processing speed deficits are needed inform to early interventions seeking to mitigate potentially contributing factors, even during frontline NHL therapy.

We identified associations between objective neurocognitive deficits and social outcomes, most notably lower educational levels, unemployment, and a higher risk of blue-collar/service-oriented employment. Similarly, associations between neurocognitive deficits and education, income, and employment status in osteosarcoma survivors[25] and employment status in the larger cohort of

cancer survivors have been reported.[8] More importantly, studies indicate that cognitive interventions, both during cancer treatment and in long-term follow-up settings, may mitigate cognitive impairment.[26-28] The impact of cognitive gains on social outcomes remains unknown, yet assessing these potential benefits should be a priority of future studies.

Like Edelmann et al,[25] we identified trends suggesting that comorbid chronic conditions are associated with neurocognitive deficits. Many conditions (eg, hypertension) are amenable to intervention, and this raises the question whether optimizing the management of comorbidities might improve survivors' neurocognitive function. Likewise, emotional distress, because of its associations with neurocognitive impairment and lower social outcomes in our study, may represent another comorbidity for which more aggressive screening practices and intervention could potentially mitigate these outcomes. Our results should heighten the awareness of previously underappreciated neurocognitive impairments in NHL survivors, and knowledge of these impairments may facilitate the early detection of and intervention for deficits in an effort to ultimately improve social outcomes for survivors. Interventional studies are needed to determine whether or not primary (eg, on-therapy exercise programs) or secondary prevention strategies (eg, early cognitive behavioral therapy or aggressive blood pressure control) can effectively mitigate these effects.

We report significant reductions across a number of HRQOL domains in NHL survivors associated with neurocognitive impairment. Comparable reports are sparse in the existing literature. Netson et al[29] identified associations between parental reports of child executive function and HRQOL after radiotherapy for a brain tumor; however, associations were less compelling between parent-reported executive function and child-reported HRQOL. In survivors of osteosarcoma, Edelmann et al[25] observed that variability in sustained attention and slower processing speeds were associated with poorer general health, whereas variability in sustained attention alone was associated with worse physical function. Our results suggest that objectively measured processing speed and survivor-reported executive function are associated with worse HRQOL among NHL survivors. If this association reflects a causal relation between impaired neurocognitive function and poorer HRQOL, then recent data supporting a trend toward improved neurocognitive function after cognitive rehabilitation[30] may provide support for early-detection and intervention strategies to potentially ameliorate HRQOL impairment in survivors.

NHL survivors have been reported to be less likely to hold professional/managerial jobs, more likely to be unemployed, and more likely to not complete high school in comparison with siblings.[8,31] Although these studies could not investigate the specific impact of neurocognitive function, the disparity in educational attainment between survivors and siblings was attenuated through the utilization of special education services.[31] Survivors in our study with higher academic scores were more likely to obtain a college degree, those with higher executive function were more likely to hold professional/managerial jobs, and those with higher processing speed were more likely to be employed (Table 2). Therefore, prompt recognition of neurocognitive deficits may provide opportunities for early cognitive interventions seeking to improve the attainment of educational and vocational goals.

Several limitations must be considered when one is interpreting these results. Survivors differed from controls with respect to sex, and all analyses were adjusted for sex, although cognitive functions do not differ by sex in the general population. Although our participation rate was 59.4%, previously reported similarities between SJLIFE participants and nonparticipants across a number of demographic, disease, and neighborhood-level statistics reassure us that our outcomes are not substantially affected by a participation bias.[32] Our cohort is the largest to report objectively measured neurocognitive function in NHL survivors; however, its size limits the frequency of individual chronic conditions and restricts investigations into the impact of individual conditions (eg, cardiomyopathy) on neurocognitive function. The cohort was also limited to English-speaking survivors; therefore, our findings may not be applicable to non–English-speaking survivors. A number of study variables (eg, treatment exposures) are subject to limitations from medical record abstraction. In addition, neurocognitive and HRQOL outcomes were collected in a simultaneous, cross-sectional manner, and this limited our ability to infer causal relations. Finally, NHL treatments have evolved in a such way that survivors treated with contemporary regimens are only beginning to enter long-term follow-up. Therefore, the generalizability of our findings to newly diagnosed children remains unknown, although they are applicable to the large population of survivors treated with prior protocols.

In conclusion, adult survivors of childhood NHL experience significantly impaired neurocognitive function, mental health, and HRQOL, which 26 years after the diagnosis are unrelated to the original treatment exposures. Neurocognitive impairment is associated with

emotional distress, lower educational attainment, unemployment, occupation, and reduced HRQOL. Our findings support the importance of ongoing surveillance for neurocognitive impairment and emotional distress in NHL survivors and should prompt investigations into early-detection and intervention strategies seeking to mitigate these effects.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Matthew J. Ehrhardt: Conceptualization, methodology, writing–original draft, supervision, project administration, investigation, writing–review/editing, and visualization. **Daniel A. Mulrooney**: Investigation, writing–review/editing, and visualization. **Chenghong Li**: Methodology, formal analysis, writing–original draft, investigation, writing–review/editing, and visualization. **Malek J. Baassiri**: Investigation, writing–review/editing, and visualization. **Kari Bjornard**: Investigation, writing–review/editing, and visualization. **John T. Sandlund**: Investigation, writing–review/editing, and visualization. **Tara M. Brinkman**: Investigation, writing–review/editing, and visualization. **I-Chan Huang**: Investigation, writing–review/editing, and visualization. **Deo Kumar Srivastava**: Methodology, formal analysis, data curation, writing–original draft, investigation, writing–review/editing, and visualization. **Kirsten K. Ness**: Data curation, investigation, writing–review/editing, and visualization. **Leslie L. Robison**: Conceptualization, methodology, resources, supervision, project administration, funding acquisition, investigation, writing–review/editing, and visualization. **Melissa M. Hudson**: Conceptualization, methodology, resources, writing–original draft, supervision, project administration, funding acquisition, investigation, writing–review/editing, and visualization. **Kevin R. Krull**: Conceptualization, methodology, resources, writing–original draft, supervision, project administration, funding acquisition, investigation, writing–review/editing, and visualization.

REFERENCES

1. Howlader N, Noon AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2013. Bethesda, MD: National Cancer Institute; 2016.
2. Bluhm EC, Ronckers C, Hayashi RJ, et al. Cause-specific mortality and second cancer incidence after non-Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. *Blood.* 2008;111:4014-4021.
3. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006; 355:1572-1582.
4. Moore BD III. Neurocognitive outcomes in survivors of childhood cancer. *J Pediatr Psychol.* 2005;30:51-63.
5. Ehrhardt MJ, Sandlund JT, Zhang N, et al. Late outcomes of adult survivors of childhood non-Hodgkin lymphoma: a report from the St. Jude Lifetime Cohort Study. *Pediatr Blood Cancer.* 2017;64:e26338.
6. Krull KR, Sabin ND, Reddick WE, et al. Neurocognitive function and CNS integrity in adult survivors of childhood Hodgkin lymphoma. *J Clin Oncol.* 2012;30:3618-3624.
7. Kadan-Lottick NS, Zeltzer LK, Liu Q, et al. Neurocognitive functioning in adult survivors of childhood non–central nervous system cancers. *J Natl Cancer Inst.* 2010;102:881-893.
8. Kirchhoff AC, Krull KR, Ness KK, et al. Occupational outcomes of adult childhood cancer survivors: a report from the Childhood Cancer Survivor Study. *Cancer.* 2011;117:3033-3044.
9. Krull KR, Annett RD, Pan Z, et al. Neurocognitive functioning and health-related behaviours in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Eur J Cancer.* 2011;47:1380-1388.
10. Kunin-Batson A, Kadan-Lottick N, Zhu L, et al. Predictors of independent living status in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer.* 2011;57:1197-1203.
11. Minard-Colin V, Brugieres L, Reiter A, et al. Non-Hodgkin lymphoma in children and adolescents: progress through effective collaboration, current knowledge, and challenges ahead. *J Clin Oncol.* 2015;33:2963-2974.
12. Krull KR, Brinkman TM, Li C, et al. Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: a report from the St. Jude Lifetime Cohort Study. *J Clin Oncol.* 2013; 31:4407-4415.
13. Hudson MM, Ness KK, Nolan VG, et al. Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort Study. *Pediatr Blood Cancer.* 2011;56:825-836.
14. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. http://survivorshipguidelines.org/. Accessed May 30, 2017.
15. Hudson MM, Ehrhardt MJ, Bhakta N, et al. Approach for classification and severity-grading of long-term and late-onset health events among childhood cancer survivors in the St. Jude Lifetime Cohort. *Cancer Epidemiol Biomarkers Prev.* 2017;26:666-674.
16. Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Compr Psychiatry.* 2007;48: 57-61.
17. Simic N, Khan S, Rovet J. Visuospatial, visuoperceptual, and visuoconstructive abilities in congenital hypothyroidism. *J Int Neuropsychol Soc.* 2013;19:1119-1127.
18. Swan GE, Carmelli D, Larue A. Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults. *Stroke.* 1998;29:2334-2340.
19. US Bureau of Labor Statistics. Occupational employment statistics, 2010. http://www.bls.gov/soc/major_groups.htm. Accessed May 17, 2016.
20. Benjamini Y, Hochberg Y. Controlling the false discovery rate—a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol.* 1995;57:289-300.
21. Jacola LM, Krull KR, Pui CH, et al. Longitudinal assessment of neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia treated on a contemporary chemotherapy protocol. *J Clin Oncol.* 2016;34:1239-1247.
22. Krull KR, Cheung YT, Liu W, et al. Chemotherapy pharmacodynamics and neuroimaging and neurocognitive outcomes in long-term survivors of childhood acute lymphoblastic leukemia. *J Clin Oncol.* 2016;34:2644-2653.
23. von der Weid N, Mosimann I, Hirt A, et al. Intellectual outcome in children and adolescents with acute lymphoblastic leukaemia treated with chemotherapy alone: age- and sex-related differences. *Eur J Cancer.* 2003;39:359-365.
24. Prasad PK, Hardy KK, Zhang N, et al. Psychosocial and neurocognitive outcomes in adult survivors of adolescent and early young adult cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2015;33:2545-2552.
25. Edelmann MN, Daryani VM, Bishop MW, et al. Neurocognitive and patient-reported outcomes in adult survivors of childhood osteosarcoma. *JAMA Oncol.* 2016;2:201-208.

26. Hardy KK, Willard VW, Allen TM, Bonner MJ. Working memory training in survivors of pediatric cancer: a randomized pilot study. *Psychooncology.* 2013;22:1856-1865.
27. Hardy KK, Willard VW, Bonner MJ. Computerized cognitive training in survivors of childhood cancer: a pilot study. *J Pediatr Oncol Nurs.* 2011;28:27-33.
28. Moore IM, Hockenberry MJ, Anhalt C, McCarthy K, Krull KR. Mathematics intervention for prevention of neurocognitive deficits in childhood leukemia. *Pediatr Blood Cancer.* 2012;59:278-284.
29. Netson KL, Ashford JM, Skinner T, et al. Executive dysfunction is associated with poorer health-related quality of life in pediatric brain tumor survivors. *J Neurooncol.* 2016;128:313-321.
30. Zeng Y, Cheng AS, Chan CC. Meta-analysis of the effects of neuropsychological interventions on cognitive function in non–central nervous system cancer survivors. *Integr Cancer Ther.* 2016;15:424-434.
31. Mitby PA, Robison LL, Whitton JA, et al. Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer.* 2003;97:1115-1126.
32. Ojha RP, Oancea SC, Ness KK, et al. Assessment of potential bias from non-participation in a dynamic clinical cohort of long-term childhood cancer survivors: results from the St. Jude Lifetime Cohort Study. *Pediatr Blood Cancer.* 2013;60:856-864.