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# The contribution of neurocognitive functioning to quality of life after childhood acute lymphoblastic leukemia†

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## Abstract

***Background*: Neurocognitive late effects after childhood acute lymphoblastic leukemia (ALL) are well-documented, but their impact on quality of life (QOL) is not well understood. In this multi-site study, we examined the relative influence of neurocognitive functioning, steroid randomization (prednisone vs. dexamethasone), and demographic characteristics on QOL in first-remission survivors of childhood ALL.**

***Methods*: Participants included 263 ALL survivors (ages 7–17 years at the time of evaluation; mean age at diagnosis 3.9 years) who were treated on similar legacy Children's Cancer Group chemotherapy protocols and did not receive cranial radiation. Children completed detailed neuropsychological performance tests. The Pediatric QOL Inventory was completed by children and their parents. Participants were a mean of 9 years from diagnosis at the time of assessment (with a range of 4 to 13 years).**

***Results*: Children and their parents reported lower mean child psychosocial QOL than healthy population norms ($p < 0.05$), but were not in the impaired range. Physical QOL was similar to population norms. Though neurocognitive difficulties were predominantly mild for the sample as a whole, neurocognitive deficits, specifically problems in verbal cognitive abilities and visual-motor integration skills, were significantly associated with poor physical ($p < 0.01$) and Psychosocial QOL ($p < 0.01$). QOL was not associated with previous steroid randomization.**

***Conclusions*: ALL survivors with neurocognitive deficits are at risk for poor QOL, with broad implications for their physical, social, and school functioning.**


## Introduction

The success of treatment for acute lymphoblastic leukemia (ALL) in childhood has improved dramatically over the years, resulting in estimated survival rates over 85% for patients treated with current therapies [1]. With this increasing success, more emphasis has been placed on understanding the long-term sequelae of diagnosis and treatment. In addition to well-documented medical late effects of treatment (e.g., osteoporosis, peripheral neuropathy, and osteonecrosis), childhood ALL survivors are at risk for neurocognitive late effects, including difficulties with attention, visual-motor function, processing speed, and working memory [2,3]. Neurocognitive consequences of ALL therapy with cranial radiation have been shown to negatively impact independent living in adulthood [4], marriage rates, [5] and employment [6]. In ALL patients who do not receive cranial radiation, neurocognitive impairments are comparatively mild. It is not known whether these milder difficulties result in meaningful differences affecting the child's quality of life (QOL).

Quality of life is a multidimensional construct measuring subjective well-being. In the context of children with chronic illness, QOL is often measured through parent and patient perceptions of the impact of illness on important functional domains. In children and adults with neurodevelopmental and neurological disorders (e.g., spina bifida, epilepsy, schizophrenia, and coronary artery bypass graft surgery), associations have been found between neuropsychological test scores and patient and parent report of QOL [7–9]. Although a large-scale study in adult survivors of childhood cancer described that treatment/diagnosis factors commonly associated with greater degrees of neurocognitive difficulty (i.e., cranial radiation therapy, CNS (central nervous system) tumors, and younger age at diagnosis) are risk factors for poor QOL after treatment [10], other studies that have used neuropsychological testing to document degree of neurocognitive difficulty after cancer treatment have not found this association with QOL [11].

Corticosteroid therapy remains an essential component of modern ALL therapy and is most commonly given as either dexamethasone or prednisone. Although studies in non-cancer populations suggest that corticosteroids contribute to cognitive difficulties [12–14], previous studies have shown that the type of steroid regimen used for

ALL treatment does not differentially impact long-term neurocognitive functioning [15,16]. However, there is reason to believe that choice of corticosteroid may affect long-term QOL. Glucocorticoids, in general, may adversely affect mood, behavior, and body shape changes in both adults [17] and children [18]. Although acute and long-term toxicities have been reported for both prednisone and dexamethasone, evidence suggests superior penetration of dexamethasone into the CNS, which could potentially impact QOL differentially, both during and after treatment. Only one small study conducted by Eiser and colleagues (2006) [19] examined the relationship between steroid randomization and QOL. They found no significant differences between the QOL of 17 children randomized to dexamethasone and 28 children randomized to prednisone evaluated during therapy. However, data from larger studies are not available and the long-term implications of different corticosteroid regimens on QOL are not known.

In general, the QOL of childhood survivors of ALL treated on modern therapy protocols without cranial radiation has not been well-studied. Past studies have been hampered by small sample sizes, heterogeneous disease samples, limited length of follow-up, and lack of use of standardized neurocognitive and QOL instruments. The current study overcomes many of these limitations. We utilize a large sample of patients with standard risk precursor B ALL who were previously enrolled on two similar Children's Cancer Group trials and underwent extensive performance-based neurocognitive testing at a mean of 9 years after diagnosis. We seek to (1) characterize the QOL of children after ALL in the Physical, Social, Emotional, and School domains, as reported by children and their parents; and (2) determine the relative contribution of neurocognitive functioning and corticosteroid randomization to QOL.

## Methods

This was a cross-sectional study of patients previously enrolled and randomized on Children's Cancer Group legacy protocols 1922 and 1952, which were open between March 1993 and August 1995 and between May1996 and February 2000, respectively. Protocol 1922 was a $2 \times 2$ factorial design in which patients with National Cancer Institute standard risk precursor B ALL were assigned randomly to (1) either prednisone or dexamethasone for the majority of therapy; and (2) either intravenous or oral 6-mercaptopurine (6-MP). Protocol 1952 was also a $2 \times 2$ factorial design in which participants were randomly assigned to (1) either intrathecal methotrexate or triple intrathecal therapy; and (2) to either oral mercaptopurine or thioguanine.

Further treatment details about these protocols have been previously published [20,21]. The institutional review board of each participating center approved the protocol and study documents. Informed consent, and assent if indicated, was obtained from all participants in accordance with the Declaration of Helsinki.

### Participants

Eligible patients had no history of CNS leukemia (and thus no cranial radiation), were at least one year from completing therapy and in continuous remission, were between 6 years and younger than 17 years at the time of evaluation, had no history of pre-existing developmental disorders (e.g., trisomy 21, developmental delay), no history of very low birth weight ($<$1500 grams), and were previously enrolled on CCG 1922 or 1952 at one of the participating 22 institutions (subset of the $>$250 sites participating on the therapeutic study). Individuals were excluded if they had been non-randomly assigned to more intensive therapy because of unfavorable cytogenetic findings or a slow response after induction. The age range was chosen to correspond to allow for consistent use of standardized neuropsychological assessment across the cohort. There were 746 eligible patients at the 22 participating sites, of which 263 (35%) enrolled on the current study and completed neurocognitive and QOL evaluations. This participation rate is consistent with other neurobehavioral studies conducted within Children's Oncology Group treatment trials during this time period, and not unexpected given the length of the test battery and the availability of resources required for testing.

### Measures/procedure

Participants underwent comprehensive neuropsychological evaluations, supervised by a licensed psychologist. As described in previous publications [15,22] evaluation was paid for by research funds at no cost to the patient. Neuropsychological performance was examined across several domains including: cognitive ability (Wechsler Intelligence Scale for Children-Fourth Edition; WISC-IV), sustained attention, response speed/consistency, and impulse control (Conners Continuous Performance Test—Second Edition), working memory (WISC-IV Working Memory Index), processing speed (WISC-IV Processing Speed Index), and visual-motor integration (Beery Test of Visual-Motor Integration), and academic achievement (Wechsler Individual Achievement Test—Second Edition—Abbreviated). All are standardized, norm-referenced measures designed for use in the age range specified by the study. Parents of participants also completed a demographic (e.g., parent education, income) and medical history survey. This questionnaire also confirmed that participants were developing normally before ALL diagnosis as an additional check for eligibility.

Parents and children completed questionnaires measuring their report of the child's Physical and Psychosocial



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(i.e., School, Emotion, Social) QOL using the Pediatric QOL Inventory (PedsQL)—4.0, standard version [23,24]. The PedsQL is a widely-used brief survey for measuring health-related QOL in childhood. Children and their parents were asked to determine how much of a problem each item has been for the child during the past 1 month on a 5-point Likert scale (with 0 being never and 4 being almost always) across the core dimensions of Physical and Psychosocial domains. The Physical domain consists of items pertaining to strength (e.g., lifting heavy items), endurance (e.g., running, walking more than one block, sports), energy level, pain, and physical activities of daily living (e.g., chores around the house, bathing/showering independently). The Psychosocial domain is comprised three scales measuring the child's Emotional functioning (e.g., mood and sleep difficulties), Social functioning (e.g., getting along with peers, keeping up with other children), and School functioning (e.g., paying attention in class, forgetfulness, keeping up with schoolwork, absences because of illness or doctor's visits). Items were reverse scored and linearly transformed to a 0–100 scale ($0=100$, $1=75$, $2=50$, $3=25$, $4=0$) such that higher PedsQL scores indicate better health-related QOL (i.e., fewer symptoms). Varni and colleagues have established at-risk cutoff scores indicating poor health-related QOL for the PedsQL 4.0 core scales, which were determined by approximating 1-standard deviation below mean scores for a normative sample of 5972 healthy children aged 5–18 years and 10,070 caregivers of children aged 2–18 years [25]. Scores were dichotomized such that scores below this cutoff score were classified as a poor QOL outcome [26].

## Results

### Participants

Demographic characteristics of the 263 participants are displayed in Table 1. Participants were a mean of 9.0 years from diagnosis at the time of assessment, with a range of 4.8 to 13.7 years. Males and females were evenly distributed; the majority were white. Participants and eligible non-participants ($n=483$) at the 22 sites did not differ in distribution of males/females ($\chi^2=0.798$, $p>0.05$) or age at diagnosis (mean = 3.9 for participants; 4.0 for non-participants, $p>0.05$). Within the two treatment studies (1922 and 1952), participants and non-participants were not statistically different on therapeutic randomization [20,21].

**Table 1.** Demographic and clinical characteristics of the sample

| | *N* = 263 |
|---|---|
| Age at diagnosis (years; mean, range) | 3.9 (4.8-13.7) |
| Age at testing (years; mean, range) | 13.1 (7.5-17.0) |
| Sex, *n* (%) | |
| Female | 120 (46%) |
| Race/ethnicity, n (%) | |
| White/non-Hispanic | 213 (81.0%) |
| Ethnic/racial minority | 44 (16.7%) |
| Missing | 6 (2.3%) |
| Household income, *n* (%) | |
| Less than or equal to $80 000 | 148 (56.3%) |
| Greater than $80 000 | 91 (34.6%) |
| Missing | 24 (9.1%) |
| Maternal education, *n* (%) | |
| Less than college graduate | 164 (62.3%) |
| College graduate or higher | 87 (33.1%) |
| Missing | 12 (4.6%) |
| Intrathecal chemotherapy regimen, *n* (%) | |
| Triple intrathecal therapy | 91 (34.6%) |
| IT-Methotrexate | 172 (65.4%) |
| Steroid chemotherapy regimen, *n* (%) | |
| Prednisone | 210 (80.2%) |
| Dexamethasone | 55 (19.8%) |

### Parent and child-report of quality of life

As summarized in Table 2, parent and child ratings of the child's total QOL were lower than population norms, with variability noted across physical and psychosocial domains. To better characterize the QOL of childhood cancer survivors, domain-specific summary scores and subscales were examined. Both parent and child ratings were significantly lower than healthy population normative data on the Psychosocial Summary Scale and School Functioning Subscale. Parent ratings were also lower than population norms for children's Emotional Functioning. However, mean ratings for our sample fell above established 'at risk' cut off scores for impaired QOL on all scales [25], suggesting that the majority of our sample was functioning within the expected range both physically and psychosocially. Ratings from approximately 20–25% of our sample ($n=66$ for parent-report and $n=52$ for child report) fell more than one standard deviation below the population mean, reflecting poor Psychosocial QOL, whereas ratings from 14% of our sample ($n=39$ for parent-report and $n=37$ for child report) reflected poor Physical QOL.

Parent and child QOL ratings were significantly ($p<0.001$) positively associated across all domains, with Pearson correlation coefficients ranging from 0.434 (Emotional QOL) to 0.585 (Psychosocial QOL). Paired *t*-tests found no significant mean differences between parent and child reported QOL with the exception of Physical QOL ($t(251)=1.98$ $p=0.049$). That is, parent-reported scores were slightly lower (mean = 83.98) than children's self-reported functioning (mean = 85.96).

### Neurocognitive functioning

As shown in Table 3, mean neurocognitive performance across domains fell within the average range, consistent with population norms. Scores were dichotomized to reflect those with or without neurocognitive impairment on each dimension, with deficit defined as attaining a



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**Table 2.** Parent and child-reported quality of life compared with healthy population norms

| | ALL survivors | Healthy norms[a] | At-risk cutoff[a] | ALL At-risk | |
|---|---|---|---|---|---|
| Scale | Mean (SD) | Mean (SD) | Score | % | *p*-value |
| Child self-report | | | | | |
| Physical health | 85.99 (13.2) | 87.77 (13.1) | 72.98 | 14.8 | 0.27 |
| Emotion function | 75.50 (18.8) | 79.21 (18.0) | 59.57 | 16.9 | 0.12 |
| Social function | 84.38 (18.3) | 84.97 (16.7) | 66.61 | 13.7 | 0.56 |
| School function | 72.64 (17.6) | 81.31 (16.1) | 62.99 | 27.8 | <0.01** |
| Psychosocial summary | 77.51 (15.2) | 81.83 (14.0) | 66.03 | 20.0 | 0.03* |
| Total QOL score | 80.46 (13.5) | 83.91 (12.5) | 69.71 | 19.8 | 0.05* |
| Parent Proxy-report | | | | | |
| Physical health | 83.90 (17.9) | 84.08 (19.7) | 63.28 | 14.1 | 0.54 |
| Emotion function | 73.22 (20.7) | 81.20 (16.4) | 63.29 | 27.4 | <0.01** |
| Social function | 82.48 (20.4) | 83.05 (19.7) | 62.07 | 16.7 | 0.56 |
| School function | 72.39 (21.7) | 78.27 (20.1) | 56.75 | 26.2 | 0.03* |
| Psychosocial summary | 76.02 (17.9) | 81.24 (15.8) | 64.38 | 25.1 | 0.01* |
| Total QOL score | 78.76 (16.7) | 82.29 (15.6) | 65.42 | 19.3 | 0.01* |

ALL, acute lymphoblastic leukemia; QOL, quality of life.
*p*-value represents difference between current sample mean and healthy population norms.
[a]Healthy population norms and 'at risk' cutoff scores defined per Varni.[21]

score falling more than one standard deviation below the population mean. Frequencies of impairment within our cohort were compared with the expected 16% in the general population. Survivors demonstrated elevated frequencies of impairment on measures of processing speed and visual-motor integration. However, frequencies of impairment did not differ significantly from population-based frequencies in verbal or nonverbal cognitive ability, working memory, academic achievement, or sustained attention. Across all neurocognitive domains measured in the present study, 40% of survivors showed a deficit in one or more areas.

## Neurocognitive, treatment, and socio-demographic predictors of quality of life

Univariate and multivariable logistic regression models were used to examine the relative contributions of neurocognitive, treatment, and socio-demographic factors to QOL. The final multivariable logistic regression model was reduced using forward selection to determine best fit. Data were analyzed with SPSS Statistics for Windows, Version 21.0 (IBM Corp, Armonk, NY). As the primary goal of these analyses was to determine the relative influence of neurocognitive functioning on QOL, and prior studies have found that neurocognitive functioning can influence self-ratings [27], only parent ratings are used below to provide a more robust test of the impact of neurocognitive late effects on QOL.

In univariate analyses (Table 4) adjusted for age at diagnosis and sex, demographic factors (ethnic/racial minority status, lower income (≤80 000), and shorter elapsed time from diagnosis) were strongly associated with poor Psychosocial QOL and Physical QOL. Corticosteroid randomization (prednisone vs. dexamethasone) was not associated with QOL. Neurocognitive factors, specifically deficits in verbal cognitive abilities (WISC-IV VCI), perceptual reasoning abilities (WISC-IV, PRI) were strongly associated with at-risk scores for both Psychosocial and Physical QOL. Visual-motor integration deficits (perceptual-motor skills; Beery VMI) were strongly associated with poor Psychosocial QOL.

Risk factors that remained significant in our multivariable model predicting poor Physical QOL included time since diagnosis (OR 2.52, 95% CI 1.06—5.98, $p = 0.037$), household income (OR 3.34, 95% CI 1.08–10.38, $p = 0.036$), and

**Table 3.** Mean neurocognitive performance and percent scoring more than one standard deviation below the population mean

| | ALL survivors | Number with deficit[a] |
|---|---|---|
| Scale | Mean (SD) | *N* (%) |
| WISC-IV | | |
| Verbal Cognitive Index | 102.13 (12.9) | 24 (9.1) |
| Perceptual Reasoning Index | 101.78 (12.9) | 23 (8.7) |
| Working Memory Index | 98.39 (14.7) | 33 (12.5) |
| Processing Speed Index | 94.58 (12.13) | 65 (24.7) |
| Full Scale IQ | 100.15 (12.22) | 24 (9.2) |
| WIAT-II | | |
| Word reading | 101.08 (12.32) | 23 (8.7) |
| Numerical operations | 100.74 (15.73) | 40 (15.2) |
| Spelling | 101.48 (14.12) | 32 (12.2) |
| Conners CPT-II | | |
| Omission errors | 46.83 (7.32) | 10 (3.8) |
| Commission errors | 49.47 (32.08) | 32 (12.2) |
| Response time | 47.33 (10.21) | 25 (9.5) |
| Variability | 45.89 (8.82) | 18 (6.8) |
| Beery visual-motor integration | 92.56 (13.27) | 67 (25.5) |

ALL, acute lymphoblastic leukemia; WISC-IV, Wechsler Intelligence Scale for Children—4th Edition; WIAT-II, Wechsler Individual Achievement Test—2nd Edition; Conners CPT-II, Conners Continuous Performance Test—2nd Edition.
[a]Deficit defined as those participants scoring more than 1 standard deviation below the population mean.



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**Table 4.** Univariate associations between child/family characteristics, treatment factors, and neurocognitive functioning with impaired quality of life

| | Physical QOL | | Psychosocial QOL | |
|---|---|---|---|---|
| | **OR (95% CI)** | ***p*-value** | **OR (95% CI)** | ***p*-value** |
| Time since diagnosis | | | | |
| ≥9 years | Referent | | Referent | |
| <9 years | 2.45 (1.17-5.10) | 0.017 | 1.43 (0.81-2.50) | 0.22 |
| Race/ethnicity | | | | |
| White | Referent | | Referent | |
| Black, Hispanic, and others | 2.58 (1.15-5.76) | 0.021 | 3.07 (1.55-6.05) | 0.001 |
| Income | | | | |
| >80 000 | Referent | | Referent | |
| ≤80 000 | 5.08 (1.72-14.9) | 0.003 | 3.27 (1.62-6.59) | 0.001 |
| Steroid chemotherapy | | | | |
| Prednisone | Referent | | Referent | |
| Dexamethasone | 0.44 (1.5-1.30) | 0.13 | 0.65 (0.31-1.40) | 0.28 |
| Verbal cognitive ability | | | | |
| No problem | Referent | | Referent | |
| Deficit | 4.49 (1.78-11.2) | 0.001 | 2.80 (1.18-6.62) | 0.019 |
| Perceptual reasoning | | | | |
| No problem | Referent | | Referent | |
| Deficit | 3.93 (1.52-9.85) | 0.001 | 3.07 (1.28-7.36) | 0.012 |
| Visual-motor skills | | | | |
| No problem | Referent | | Referent | |
| Deficit | 2.03 (0.96-4.21) | 0.062 | 2.87 (1.56-5.30) | 0.001 |
| Attention variability | | | | |
| No problem | Referent | | Referent | |
| Deficit | 1.12 (0.31-4.13) | 0.062 | 2.93 (1.12-7.93) | 0.029 |

OR, odds ratio; QOL, quality of life.
Odds ratio of reporting a poor QOL outcome compared with a more positive QOL outcome, adjusted for age at diagnosis and sex. ORs greater than 1 indicate a higher likelihood of achieving poor outcome.

children's verbal cognitive abilities (OR 5.01 95% CI 1.75–14.6, $p = 0.005$) such that children who were within 9 years from diagnosis, had lower household income (≤80 000), or had a deficit in verbal cognitive abilities were more likely to have poor Physical QOL. Multivariable models were used to examine the unique contributions of treatment, demographic, and neuropsychological factors to School, Emotional, and Social domains, which comprise the broader Psychosocial QOL summary scale. Risk factors that remained significant in multivariable models for poor School QOL included male sex (OR 3.47, 95% CI 1.74–6.93, $p = 0.001$), deficit in verbal cognitive abilities (OR 3.33, 95% CI 1.43–9.68, $p = 0.027$) and deficit in visual-motor integration skills (OR 3.13, 95% CI 1.58–6.22, $p = 0.001$). Within the School QOL domain, item analysis found that parents of males endorsed significantly more difficulties on items sampling forgetfulness ($t(259) = 2.78$, $p < 0.01$) and problems keeping up with schoolwork ($t(258) = 4.45$, $p < 0.001$) than females. Risk factors for poor Social QOL included lower household income (OR 2.90, 95% CI 1.11–7.59 $p = 0.03$) and deficit in visual-motor integration skills (OR 2.36, 95% CI 1.19–5.28, $p = 0.020$). Only lower household income remained a significant predictor of poor Emotional QOL (OR 2.18, 95% CI 1.13–4.20, $p = 0.02$).

## Discussion

To our knowledge, this study is the largest to date that characterized parent and child-report of QOL after acute lymphoblastic leukemia in children who were treated with chemotherapy alone. The 263 patients in our study were a mean of 9 years after diagnosis when they underwent standardized QOL assessment and neurocognitive assessment by psychologists. The majority of survivors in our multisite study reported good QOL, at levels that tend to approximate healthy population norms in some domains. Ratings were significantly lower than population norms on parent and child-reported ratings of children's psychosocial functioning, specifically the school functioning subscale, reflecting concern regarding school performance (e.g., forgetfulness, inattention, keeping up with schoolwork, and school attendance). Parent ratings were also lower than population norms for child's emotional functioning reflecting more reported concern regarding their child's worry, sleep difficulty, or sadness/irritability. Nonetheless, mean QOL scores for ALL survivors were above the recognized cut off scores for impaired QOL and generally reflect good functioning.

This study also identified subgroups of survivors who are at risk for poor QOL, and highlights the role of



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neurocognitive deficits and economic disparity in QOL after ALL. In our sample, 25% of ALL survivors fell below the established threshold for poor Psychosocial QOL and 14% reported poor Physical QOL. Whereas mean neurocognitive functioning in our cohort was in the average range consistent with population norms, 25% of our sample scored at least one standard deviation below the mean on processing speed and/or visual-motor integration tasks, both of which require significant graphomotor skills. Forty percent of our sample experienced this degree of difficulty in at least one neurocognitive domain, consistent with previous studies [3,28].

In multivariable logistic regression analyses, neurocognitive functioning was strongly associated with both Physical and Psychosocial QOL, whereas diagnostic and treatment factors (e.g., choice of corticosteroid regimen, age at diagnosis) were not. Survivors with a deficit in verbal cognitive abilities were much more likely to be rated by their parents as having poor QOL in Physical and School domains. Unlike studies in adult survivors of adult cancers, which have found no association between time since diagnosis and QOL [29], in our cohort, children with poor Physical QOL were much more likely to be closer to diagnosis. The relationship between neurocognitive functioning and Physical QOL is not unexpected, as other studies have found survivors with cognitive deficits to be less physically active [30], with implications for strength, endurance, and performance of activities of daily living tapped by the Physical QOL scale.

Those with poor School QOL were significantly more likely to be male and three times more likely to have deficits in verbal cognitive abilities and visual-motor integration skills. Whereas prior studies have found that females are at greater risk for neurocognitive deficits following cancer treatment, our findings suggest that males are more likely to have functional difficulties in school tapped by the School QOL scale (i.e., problems keeping up with school work, and forgetting things). Verbal cognitive abilities and visual-motor integration skills are also important factors for school success given that the majority of classroom instruction is language-based and visual-motor skills have implications for children's handwriting/note-taking. Neurocognitive functioning was also associated with problems with children's Social QOL, but not significantly related to children's Emotional functioning.

As in the general population [31,32], socio-economic characteristics of the family also play a role in QOL after childhood cancer. Specifically, lower household income was associated with poor Physical QOL, as well as poor Social and Emotional QOL. Although beyond the scope of present study, survivors from lower income households may have more difficulties accessing resources necessary for their optimal physical functioning (e.g., physical therapy) and emotional-social health (e.g., social-work services and psychotherapy) or experience a greater number of family stressors related to lower income, which may contribute to this association. The economic impact of cancer on families will be important to examine in prospective studies, in order to understand when and how best to intervene to promote QOL. A structured approach to psychosocial assessments using instruments such as the Psychosocial Assessment Tool (PAT 2.0, [33] which include questions about family financial difficulties and resources) may be useful to more readily identify families at risk for poor QOL. Within institutions, targeted social work driven interventions may be useful to reduce barriers to obtaining services to promote the physical functioning and psychosocial well-being of childhood cancer survivors from socio-economically at-risk families. On a larger scale, policy efforts to equalize disparities by improving access to care and surveillance for low-income patients over the course of survivorship may also be important for QOL.

Our study should be understood in the context of potential limitations. Our sample is under-represented in terms of racial minority survivors. Although univariate analyses found that non-white survivors were more likely to have poor QOL than whites, this relationship did not hold when income was included in multivariable analysis. It is possible that the low numbers of non-white survivors in this study limited our power to see this association, or that household income was the predominant driver of this relationship. Potential racial disparities in QOL after childhood cancer should be explored in more diverse samples to determine whether blacks, Hispanics, or other ethnic subgroups may face unique barriers to QOL. Additionally, although we found that children who are further from diagnosis had better Physical QOL, the cross-sectional design of our study prevents conclusions we can draw regarding changes in QOL over time and whether experiences closer to diagnosis and during treatment can continue to influence QOL long after treatment has ended. Future prospective studies should also examine the socio-economic impact of cancer on families to better understand whether disparities may have pre-dated cancer diagnosis, were present at the time of diagnosis, or developed over the course of treatment/survivorship and represent the economic toll of cancer on QOL. Such information will be useful for guiding intervention development and timing/delivery of interventions for at-risk families.

Although neurocognitive difficulties after ALL are often mild for the majority of survivors, our findings suggest that neurocognitive functioning after treatment plays an important role in their QOL. Surveillance for neurocognitive difficulties in survivors is necessary so that appropriate services can be provided to those with deficits. While most cognitive rehabilitation approaches for neurocognitive late effects focus on improving attention and working memory skills, our findings



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suggest that targeted interventions to address visual-motor integration difficulties (such as occupational therapy) and the development of verbal cognitive skills (e.g., learning support for vocabulary knowledge and word reasoning) may be useful for childhood ALL survivors with implications for their QOL. Ongoing research efforts are needed to develop prevention and early intervention strategies to support these areas of neurocognitive functioning in children with ALL in order to optimize QOL after treatment. Our study also suggests that children from socioeconomically disadvantaged families are particularly vulnerable to poor QOL after treatment. Further attention should be paid to the assessment of socioeconomic risk factors to help at-risk families overcome barriers and access resources needed to optimize their child's physical and psychosocial functioning.

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## Author Contribution

A. K-B. analyzed data, performed research and prepared the manuscript. N. K-L and J. P. N. designed and performed research, interpreted study results, and prepared the manuscript.

## Conflict of interest

The authors have declared no conflicts of interest.

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