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Health-related quality of life of adolescent and young adult survivors of childhood brain tumors

Lamia P. Barakat[1,2]*, Yimei Li[1,2], Wendy L. Hobbie[1,3], Sue K. Ogle[1], Thomas Hardie[4], Ellen M. Volpe[5], Margo M. Szabo[6], Maureen Reilly[1] and Janet A. Deatrick[3]

[1]*The Children's Hospital of Philadelphia, Philadelphia, PA, USA*
[2]*Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA*
[3]*School of Nursing, University of Pennsylvania, Philadelphia, PA, USA*
[4]*Drexel University, Philadelphia, PA, USA*
[5]*University of Buffalo, Buffalo, NY, USA*
[6]*West Virginia University, Morgantown, WV, USA*

**Correspondence to:*
Division of Oncology, The Children's Hospital of Philadelphia, 3501 Civic Center Blvd., 10303 CTRB, Philadelphia, PA 19104, USA.
E-mail: barakat@email.chop.edu

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Abstract

***Objective*: Our aim was to expand research on predictors of health-related quality of life (HRQOL) for adolescent and young adult survivors of childhood brain tumors who are not living independently by evaluating the mediating role of family functioning in the association of disease severity/treatment late effects with survivor self-report and caregiver-proxy report of physical and emotional HRQOL.**

***Methods*: Mothers ($N = 186$) and their survivors living at home ($N = 126$) completed self-report and caregiver-proxy report of physical and emotional HRQOL. Mothers completed family functioning measures of general family functioning, caregiving demands, and caregiver distress. Medical file review and caregiver report were used to evaluate disease severity/treatment late effects.**

***Results*: Using structural equation models, family functioning was adjusted for sociodemographic factors. Disease severity/treatment late effects had significant direct effects on self-report and caregiver-proxy report of physical and emotional HRQOL. Family functioning had a significant direct effect on caregiver-proxy report of physical and emotional HRQOL, but these findings were not confirmed for self-report HRQOL. Model-fit indices suggested good fit of the models, but the mediation effect of family functioning was not supported.**

***Conclusions*: Disease severity/treatment late effects explained self-report and caregiver-proxy report of physical and emotional HRQOL for these adolescent and young adult survivors of childhood brain tumors. Family functioning was implicated as an important factor for caregiver-proxy report only. To enhance physical and emotional HRQOL, findings underscore the importance of coordinated, multidisciplinary follow-up care for the survivors who are not living independently and their families to address treatment late effects and support family management.**

Background

Brain tumors are the second most common childhood cancer diagnosis in the USA with an incidence of 41.4 per 1,000,000. With advances in surgical, chemotherapy, and cranial radiation techniques and supportive care, survival rates for children with brain tumors have steadily increased to over 70% since 1975 [1]. Exposure to such treatments puts survivors at risk for a host of late effects, including cardiac, endocrine, sensory, neurocognitive, and psychological conditions [2,3], which limit survivor health-related quality of life (HRQOL) [4–6].

A multidimensional construct, HRQOL encompasses the subjective evaluation of general, physical, emotional, spiritual, and social functioning and extends to include aspects of the illness and developmental stage [7,8]. For adolescent and young adult (AYA) survivors of cancer, HRQOL includes reproductive/sexual health, physical appearance, and resilience [6]. In comparison with all childhood cancer survivors, survivors of childhood brain tumors report the poorest HRQOL [7,9], with impairments in multiple domains of psychosocial functioning, including education, employment, marital status, ability to drive, and living independently [2]. Survivors of childhood brain tumors also exhibit depression [10].

Treatment-related variables and neurocognitive late effects are implicated in studies examining factors associated with HRQOL. Tumor site, cranial radiation, tumor progression, and relapse have been associated with poorer HRQOL [9,11]. The Childhood Cancer Survivor Study documented lower rates of marriage and employment in brain tumor survivors treated with radiation therapy [12]. Chemotherapy has also been linked to increased behavioral problems in survivors of pediatric brain tumors

[13]. Survivors with poorer neurocognitive functioning reported lower rates of employment, marriage, educational attainment, and lower income levels [14]. The addition of treatment modalities increases the negative effect of treatment on physical HRQOL [7].

Sociodemographic variables have also been associated with the adaptation of survivors of childhood brain tumors. Age at diagnosis is inversely associated with HRQOL in survivors of childhood cancers, including brain tumor survivors [15], and higher socioeconomic status has been associated with higher adaptive functioning and HRQOL in brain tumor survivors [15,16]. Compared with male survivors, female survivors report poorer HRQOL [17] and more psychological distress [10].

Studies have shown that survivorship strains families and influences family functioning, parenting stress, and parent adjustment [18–20]. Parents of childhood brain tumor survivors have elevated levels of posttraumatic stress and general psychological distress [18], and parents of children treated with cranial radiation experience greater psychological distress compared with parents of children who did not require cranial radiation [19]. Furthermore, high levels of uncertainty and caregiver demands persist for parents of children off treatment for brain tumors [20]. Peterson and Drotar [21] proposed a model in which disease and treatment variables may influence both the family's adaptation to the child's illness and the child's neurocognitive and psychosocial outcomes. Simultaneously, family adaptation to the illness may affect family functioning and child outcomes. Consistent with this model, Carlson-Green and colleagues [16] found that children from families who experienced less stress at the time of diagnosis had fewer behavioral problems. Another study among adolescents undergoing treatment for cancer, including brain tumors, demonstrated that family functioning had a significant association with HRQOL [22].

Advances in research on families and adaptation are insufficient, however, because of inattention to disease sequelae and lack of specificity to survivors of childhood brain tumors, who are particularly at risk for poor HRQOL and limited independence. From the current study sample, survivor health was associated with caregiver competence, and general family functioning mediated the association of caregiver demand with caregiver competence [23]. Further, data from a pilot study support family functioning as a mediator of neurocognitive functioning and HRQOL for childhood brain tumor survivors [24]. We examined the relative roles of disease severity/treatment late effects and family functioning in explaining the HRQOL for a sample of AYA survivors of childhood brain tumors with restricted independence with the expectation that family functioning would have both direct and indirect relationships to physical and emotional HRQOL.

Methods

Participants

As part of a larger study describing family management, 186 mothers (caregivers) of AYA survivors of childhood brain tumors completed measures of disease severity/treatment late effects, family functioning, and caregiver proxy of survivor HRQOL, and 126 of their corresponding survivors of childhood brain tumors completed a measure of self-reported HRQOL [23]. Survivors were as follows: (a) aged 14–39 years; (b) at least 5 years from initial cancer diagnosis and 2 years from discontinuation of treatment; and (c) living at least part time, or at least 50% of the time over the past 6 months, in the same household as the mother. Survivors with a genetic basis for the brain tumor (i.e., neurofibromatosis), a diagnosis of mental retardation or developmental delay prior to the cancer diagnosis, or married or living in a partnered relationship were excluded.

Recruitment was conducted in an academic hospital in a large northeastern city through a twofold strategy: (a) 1077 mailings from a large database of brain tumor cases that occurred over the past 30 years and (b) 63 face-to-face contacts of screened cases identified in neuro-oncology and survivorship outpatient clinics. After initial contact by mail or in clinic, 384 mothers provided initial agreement to be contacted for telephone screening (30% responded to the mailings and 90% to clinic contacts). Of these, 190 mother–survivor pairs were eligible; 186 mothers consented and completed data collection, and 126 of their survivors completed measures of HRQOL. Twenty-nine survivors of the 186 mothers refused participation, and the remaining nonparticipants were unable to complete the assessment. For further information, refer to Deatrick *et al*. [23].

Measures

Disease and treatment-related variables

Intensity of treatment rating [25], a scale that provides an objective rating of the child's treatment intensity based on the number and combination of therapies received, was adapted for a pediatric brain tumor population [26]. It included the following ratings: (a) minimal = resection only; (b) moderate = radiation or chemotherapy ± resection; and (c) intensive = radiation and chemotherapy ± resection. High inter-rater reliability and face validity of these ratings have been reported [26]. Data were abstracted from medical charts and rated by a pediatric oncology nurse practitioner (W. L. H.) and a pediatric oncologist specializing in survivorship blind to the participant's identity (inter-rater reliability kappa = 0.97).

Medical late effects rating, a scale that provides an objective rating of the late effects of the child's cancer treatment, was adapted to a pediatric brain tumor population

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[26]. It included the following ratings: (a) no limitations = no activity limitations and no special medical attention required; (b) mild restrictions = mild conditions that require some medical attention (e.g., mild hearing loss); (c) moderate restrictions = significant medical attention required on a regular basis (e.g., seizures poorly controlled with medication); and (d) severe restrictions. Data were abstracted from medical charts and rated by a pediatric oncology nurse practitioner (W. L. H.) and a pediatric oncologist specializing in survivorship blind to the participant's identity (inter-rater reliability kappa = 0.94).

Mother rating of cognitive functioning post-diagnosis was obtained by an item on a demographic questionnaire on which the mother was instructed to rank from 1 to 10 her perception of the survivor's ongoing cognitive/academic disabilities after cancer treatment.

Past life threat and current life threat ratings were constructed from two items from the *Assessment of Life Threat and Treatment Intensity Questionnaire*, a seven-item measure using a 5-point Likert-type scale (disagree–agree) [27]. Items used to reflect past threat and current threat, 'My child could have died from his/her cancer' and 'My child could still die from his/her cancer', have been used for brain tumor survivors to predict psychological outcomes [26].

Family functioning variables

Bakas Caregiver Outcomes Scale (BCOS) is a 15-item measure designed to examine changes in caregivers' physical health, subjective well-being, and social functioning as a result of caring for a survivor of a childhood brain tumor [28]. Mothers rated items on a 7-point Likert-type scale (−3 = changed for the worse to +3 = changed for the better). The BCOS has demonstrated acceptable reliability and validity [28]. The mean total score of the revised BCOS was used in the current study; $\alpha = 0.87$.

Family Assessment Device (FAD) is a 60-item measure that evaluates family functioning across seven subscales [29]. Mothers rated items on a 4-point Likert-type scale; lower scores indicate better family functioning. The FAD has demonstrated acceptable reliability and validity [30]. The general family functioning subscale was used; $\alpha = 0.89$.

Brief Symptom Inventory (BSI) is a 53-item measure that produces three global indices of psychological distress [31]. Each item is rated on a 5-point Likert-type scale over the past 7 days with lower scores indicating less distress. This study used the global severity index; *t*-scores are reported. The BSI has evidenced high test–retest reliability [31], and the global severity index has been used to evaluate psychological distress in parents of pediatric brain tumor survivors [18]. Cronbach's alpha for this study was 0.96.

Pediatric Oncology Quality of Life Scale is a 21-item measure that was used to assess two subscales of cancer-specific HRQOL: physical and emotional [32]. Items are rated on a 7-point Likert-type scale; lower scores indicate better HRQOL. The current response subscale was not used because all participants were off treatment, and an item regarding school was imputed for the 50 participants who no longer attended school. The measure was developed with data from children, parents, and providers, and subsequent research supports the reliability and validity [33]. Cronbach's alpha for the physical subscale was 0.89 for caregiver-proxy report and 0.74 for self-report. Cronbach's alpha for the emotional subscale was 0.79 for caregiver-proxy report and 0.80 for self-report.

Procedures

Mothers and survivors aged 18 years or older completed informed consent, and survivors aged 14–17 years

Table 1. Sample demographics ($N = 186$ mothers of survivors of childhood brain tumors)

Variable	*n* (%)	Mean (*SD*)
Survivor age (in years)		20.5 (5.3) Range = 14–39
Survivor employment		
In school only	74 (39.8)	
Employed only	36 (19.3)	
Employed and in school	42 (22.6)	
Not employed/not in school	33 (17.7)	
Survivor gender—male	105 (56.5)	
Mother's ethnicity—Hispanic	7 (3.7)	
Mother's race		
White	165 (88.7)	
African American	17 (9.1)	
Asian or Pacific Islander	4 (2.1)	
Mother's marital status		
Married	147 (79.0)	
Single/divorced/widowed	39 (21.0)	
Mother's highest education level		
High school/vocational or less	54 (29.0)	
Some college	40 (21.5)	
College	54 (29.0)	
Graduate school	33 (17.7)	
Other	5 (2.7)	
Survivor insurance		
Insured (private, public, or both)	180 (96.8)	
Noninsured	6 (3.2)	
Family income		
Less than $20,000	9 (4.8)	
Between $20,000 and 75,000	57 (30.6)	
Greater than $75,000	110 (59.1)	
Not reported	10 (5.4)	
Diagnosis		
Low-grade glioma	94 (50.5)	
Primitive neuroectodermal tumor/medulloblastoma	51 (27.4)	
Craniopharyngioma	14 (7.5)	
Other	27 (14.5)	
Years since completion of treatment		12.7 (6.3) Range = 5–39

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completed assent with one of four trained graduate research assistants via telephone. Measures were completed via telephone interview, and each participant who completed the telephone interview received $20. Interviews with caregivers averaged 85 min; interviews with survivors averaged 34 min. This study was approved by the appropriate institutional review boards.

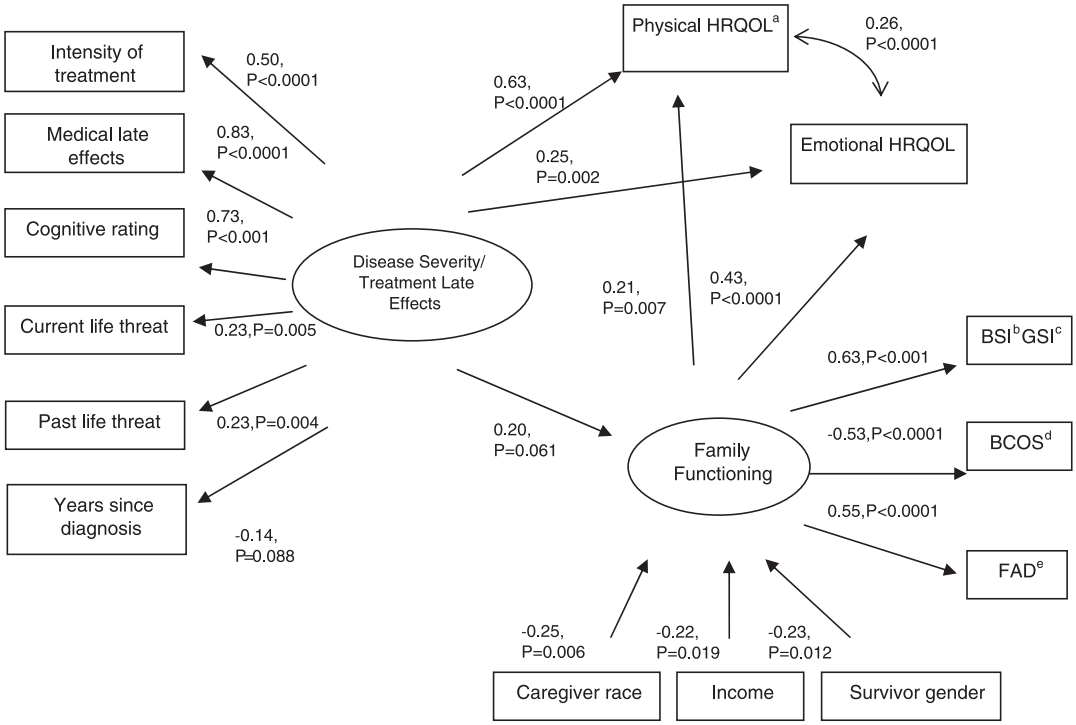
Table 2. Description of study variables

Variable	Mean (*SD*)	Range
Intensity of treatment rating	2.33 (1.24)	1–3
Medical late effects rating	2.51 (0.88)	1–4
ALTTIQ		
Past life threat	8.35 (1.86)	2–10
Current life threat	2.58 (1.60)	1–5
BCOS total score	63.73 (14.1)	27–105
FAD general functioning subscale	1.75 (0.45)	1–3.5
BSI global severity index	51.31 (13.6)	30–80
POQOL caregiver proxy		
Physical subscale	25.05 (12.68)	9–57
Emotional subscale	14.25 (7.89)	6–41
POQOL self-report		
Physical subscale	12.52 (6.47)	6–38
Emotional subscale	21.41 (9.93)	9–56

ALTTIQ, Assessment of Life Threat and Treatment Intensity Questionnaire; BCOS, Bakas Caregiver Outcomes Scale; FAD, Family Assessment Device; BSI, Brief Symptom Inventory; POQOL, Pediatric Oncology Quality of Life Scale.

Data analysis

Sociodemographics, disease severity/treatment intensity, and family functioning variables were summarized (Tables 1 and 2). Separate linear regression models were constructed for three measures of family functioning (BCOS, FAD, and BSI), with the sociodemographic predictors of mother's race, ethnicity, marital status, education level, and income as well as survivor's age, gender, and insurance. Significant variables were further adjusted in the subsequent structural equation models (SEM). SEM were used to test the hypothesized relationships among three latent factors: disease severity/treatment late effects (intensity of treatment rating, medical late effects rating, mothers' rating of cognitive function post-diagnosis, current life threat and past life threat ratings, and age at diagnosis), family functioning, and survivor self-report and caregiver-proxy report HRQOL. The model was estimated using maximum likelihood method, and standardized parameter estimates were reported. Multiple fit indices were used to assess the model fit [34]. Indications of good model fit are as follows: the ratio of chi square over degrees



[a] HRQOL – health related quality of life
[b] BSI – Brief System Inventory
[c] GSI – Global Severity Index
[d] BCOS – Bakas Caregiver Outcome Scale
[e] FAD – Family Assessment Device

Figure 1. Final structural equation model for caregiver-proxy health-related quality of life ($N = 186$)

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of freedom (df) < 2, adjusted goodness-of-fit index ($AGFI$) ≥ 0.9, comparative fit index (CFI) ≥ 0.9, and root-mean-square error of approximation ($RMSEA$) < 0.06. Two SEM were fitted: caregiver-proxy HRQOL (N = 186) and self-report HRQOL (N = 126). All analyses were conducted in SAS 9.2 (SAS Institute Inc., Cary, NC, USA). A two-sided p-value <0.05 was considered statistically significant.

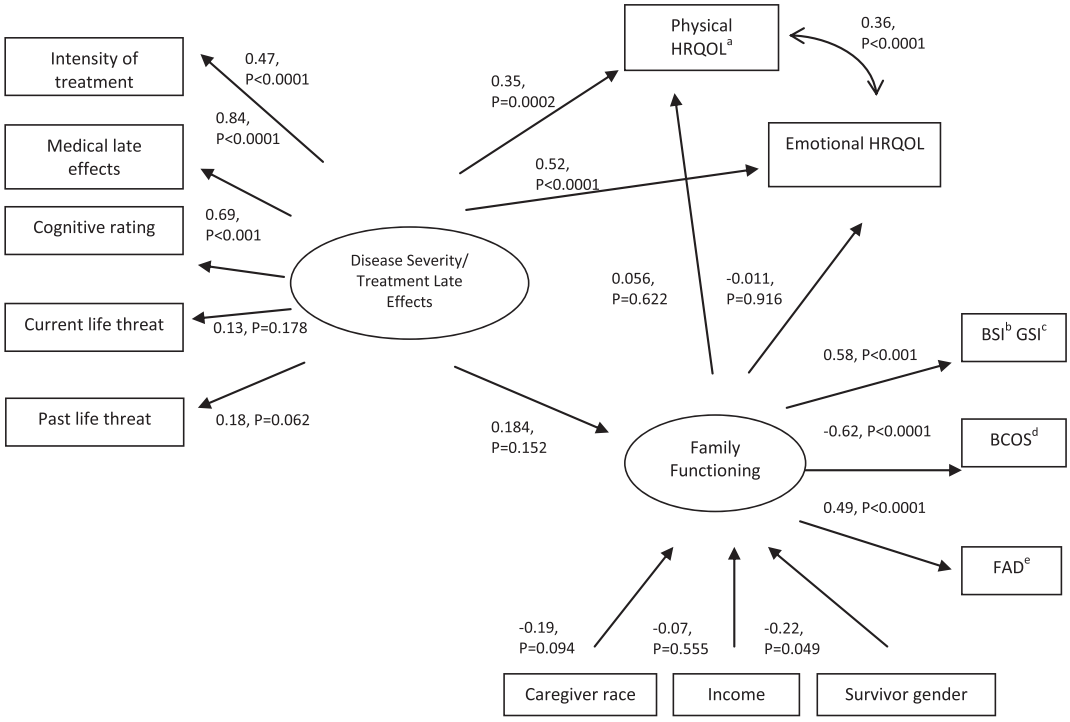
Results

Sample description

Survivors of the mother participants had an average age of 21 years and were predominantly male (57%), insured (97%), and in school and/or work (82%) (Table 1). Caregivers were predominantly White (88.7%) and non-Hispanic (96.3%) and had completed some college (22%), college (29%), or graduate school (20%). The majority of survivors were diagnosed with low-grade gliomas (51%). Years since diagnosis were on average 12.7 years.

Preliminary analyses

In the linear regressions, of mother's race, ethnicity, marital status, education level, and income and survivor's age, gender, and insurance, only mother's race and income and survivor's gender were significantly associated with family functioning measures. Family functioning was better for non-White caregivers (p = 0.006), higher income families (p = 0.019), and male survivors (p = 0.012). Mean physical HRQOL was 25.05 (SD = 12.68; range = 9–57) for caregiver-proxy report and 12.52 (SD = 6.47; range = 6–38) for survivor self-report; caregiver-proxy report and survivor self-report of physical HRQOL had an intraclass correlation of 0.466. On the basis of Pediatric Oncology Quality of Life Scale norms, mean parent rating of physical HRQOL was similarly reported as 25.9 (SD = 13.7) [33]. Mean emotional HRQOL was 14.25 (SD = 7.89; range = 6–41) for caregiver-proxy report and 21.41 (SD = 9.93, range = 9–56) for survivor self-report; caregiver-proxy report and survivor self-report had an intraclass correlation of 0.386. Bijttebeir and colleagues reported that the mean parent rating of emotional HRQOL was 15.4 (SD = 6.8); survivors of childhood brain tumors rated themselves with higher physical but lower emotional HRQOL than other pediatric oncology patients [33].



[a] HRQOL – health related quality of life
[b] BSI – Brief System Inventory
[c] GSI – Global Severity Index
[d] BCOS – Bakas Caregiver Outcome Scale
[e] FAD – Family Assessment Device

Figure 2. Final structural equation model for survivor self-report health-related quality of life (N = 126)

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Testing the hypothesized model

Caregiver-proxy health-related quality of life

All fit indices suggested good fit of the SEM: chi-square statistic is 105.1 with $df = 70$, $AGFI = 0.88$, $CFI = 0.91$, and $RMSEA = 0.05$. All the measures had significant loadings on the latent constructs except for age at diagnosis (-0.14 with a p-value of 0.088). Disease severity/treatment late effects had a large direct effect on caregiver-proxy physical HRQOL and a moderate direct effect on caregiver-proxy emotional HRQOL. The effect of disease severity/treatment late effects on family functioning was not significant. Family functioning had a moderate direct effect on caregiver-proxy physical and emotional HRQOL. The small indirect effect of family functioning was not statistically significant ($p = 0.098$ for physical HRQOL and $p = 0.078$ for emotional HRQOL) (Figure 1).

Survivor self-reported health-related quality of life

Age at diagnosis was removed from disease severity/treatment late effects because the loading was very small and not significant. All fit indices suggested good fit of the SEM: chi-square statistic is 78.4 with $df = 58$, $AGFI = 0.87$, $CFI = 0.90$, and $RMSEA = 0.05$. All the measures had significant loadings on the latent constructs except for current life threat rating and past life threat rating. Race and income's effects on family functioning were not significant for the self-reported HRQOL model. Disease severity/treatment late effects had a moderate direct effect on self-reported physical HRQOL and a large direct effect on self-reported emotional HRQOL. However, the effect of disease severity/treatment late effects on family functioning was not significant, and family functioning had almost no effect on self-reported HRQOL; mediation was not supported (Figure 2).

Conclusions

Adolescent and young adult survivors of childhood brain tumors are at risk for poor HRQOL. This study explored the contribution of family functioning to understanding HRQOL relative to the contribution of disease severity/treatment-related late effects as suggested by Peterson and Drotar [21]. Because many survivors of childhood brain tumors do not live fully independently, involvement of their family, and consequently their family's functioning, is likely critical to improving HRQOL. Findings support the importance of disease and treatment variables in understanding caregiver-proxy report and survivor self-report of HRQOL, with particularly strong effects for physical HRQOL. Family functioning had a significant main effect on caregiver-proxy report of physical and emotional HRQOL. Contrary to expectations, family functioning was not associated with survivor self-report of HRQOL. Study findings have implications for future study and clinical care of AYA survivors of childhood brain tumors who experience increased dependence on families.

Disease severity/treatment late effects remain a powerful influence on survivors' functioning after cancer treatment has ended [9,11]. Multiple variables were used to evaluate disease severity/treatment late effects including objective indicators as well as mothers' perceptions of life threat and changes in neurocognitive functioning due to the tumor and treatment. This measurement approach highlights that both the objective treatment and the subjective experience of childhood brain tumors are central to understanding functional outcomes and general adaptation post-tumor treatment.

The role of family functioning in physical and emotional HRQOL of AYA survivors of childhood brain tumors was supported for caregiver-proxy report only. Considering that family functioning was composed of general family functioning, perceived caregiving demands, and maternal distress, there are various mechanisms to explain the effect for proxy report. Caregiver-report measures comprised family functioning, which can explain the association with only caregiver-proxy HRQOL. Consistent with the Peterson and Drotar model [21], general family functioning may serve to promote survivor functioning by creating a nurturing environment in which caregivers provide resources, structure, and support. Similarly, family functioning (low perceived demands and low distress) combined with caregiver adaptation (high caregiver competence) may facilitate informal parenting strategies and formal interventions that compensate for neurocognitive impairments, thereby providing the scaffolding needed to promote HRQOL for survivors [23,24]. Family management of medical late effects, which may be integral to the survivor's perceived HRQOL, should be incorporated into future research to further understanding of how family environments nurture HRQOL in the survivorship phase [35].

The moderate intraclass correlations between self-report and caregiver-proxy report of survivor HRQOL are consistent with the literature [36–38]. Caregiver-proxy reports indicated that physical HRQOL was worse than emotional HRQOL, whereas survivors self-reported the inverse. Particularly for emotional HRQOL, questions are raised as to the extent to which HRQOL self-report versus proxy report ratings are measuring different aspects of functioning, resulting in different associations with family functioning. Importantly, neurocognitive late effects may influence survivor self-perceptions, resulting in less realistic self-evaluation or a focus on single events versus overall HRQOL [36]. It should also be acknowledged that the associations across caregiver-report variables may be the result of a negative (or positive) response style on the part of mothers.

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A critical area for clinical research will be to focus attention on enhancing HRQOL measurement for survivors of childhood brain tumors and other young adults with neurocognitive challenges [37]. Items that are cancer relevant, however, must remain part of HRQOL assessments. Goal-based measures or measures of HRQOL that account for current developmental level, neurocognitive late effects, and areas of functioning important to survivors can potentially address these gaps. Although sample characteristics are similar to those reported in the Childhood Cancer Survivor Study [12], evaluation of the model prospectively incorporating multiple reporters of family functioning and sociodemograpically diverse samples will provide richer data that can better inform preventive interventions. Because the inclusion/exclusion criteria for this study intentionally focused on survivors with functional limitations, results may vary for brain tumor survivors with few significant late effects, who are more likely to live independently [2,4]. Research indicates that in two-parent families, it is important to consider the role of fathers in caregiving and the role of mother–father mutuality in the caregiving environment, which were not considered in this study [39].

Consistent with Children's Oncology Group long-term follow-up guidelines for survivors of childhood cancers [40], this study underscores the importance of follow-up in a survivorship clinic to offer coordinated, multidisciplinary care that can address the multiple contributors to poor HRQOL for survivors of brain tumors while addressing caregiver needs and family functioning. In terms of disease severity/treatment late effects, survivorship care offers health education, targeted surveillance, and expertise in addressing chronic conditions that result from cancers and treatment. Given our prior findings linking survivor health to caregiver demands and competence [22], survivorship care that incorporates family management of late effects may also address perceived caregiver demand and family functioning.

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