original reports

Associations of Symptom Clusters and Health Outcomes in Adult Survivors of Childhood Cancer: A Report From the St Jude Lifetime Cohort Study

Hyewon Shin, PhD[1]; William N. Dudley, PhD[2]; Nickhill Bhakta, MD, MPH[3,4]; Madeline R. Horan, PhD[5]; Zhaoming Wang, PhD[5]; T. Robin Bartlett, PhD[6]; Deokumar Srivastava, PhD[7]; Yutaka Yasui, PhD[5]; Justin N. Baker, MD[4]; Leslie L. Robison, PhD[5]; Kirsten K. Ness, PT, PhD[5]; Kevin R. Krull, PhD[5,8]; Melissa M. Hudson, MD[4,5]; and I-Chan Huang, PhD[5]

abstract

PURPOSE To identify symptom clusters among adult survivors of childhood cancers and test associations with health-related quality of life (HRQOL) and physical and neurocognitive performance.

METHODS This cross-sectional study included 3,085 survivors (mean age at evaluation 31.9 ± 8.3 years; mean years from diagnosis 28.1 ± 9.1) participating in the St Jude Lifetime Cohort Study. Survivors self-reported the presence of 37 symptoms capturing 10 domains (cardiac, pulmonary, sensory, motor/movement, nausea, pain, fatigue, memory, anxiety, and depression). The Short Form-36's Physical/Mental Component Summaries assessed HRQOL; the Physical Performance Test evaluated physical performance; and neurocognitive batteries tested attention, processing/psychomotor speed, memory, and executive function. Latent class analysis identified subgroups of survivors experiencing different patterns of symptom burden (ie, symptom clusters). Multivariable regression models identified risk of cluster membership and tested associations with health outcomes.

RESULTS Four symptom clusters were identified including cluster 1 (prevalence 52.4%; low physical, somatization, and psychologic domains), cluster 2 (16.1%; low physical, moderate somatic, and high psychologic domains), cluster 3 (17.6%; high physical, moderate somatic, and low psychologic domains), and cluster 4 (13.9%; high in all three domains). Compared with cluster 1, survivors in cluster 4 were more likely to have less than high school education (odds ratio [OR], 7.71; 95% CI, 4.46 to 13.31), no insurance (OR, 1.49; 95% CI, 1.04 to 2.13), and exposure to corticosteroids (OR, 1.76; 95% CI, 1.02 to 3.03); survivors in cluster 3 were more likely to have received platinum agents (OR, 2.22; 95% CI, 1.34 to 3.68) and brain radiation ≥ 30 Gy (OR, 3.99; 95% CI, 2.33 to 6.86). Survivors in cluster 4 reported the poorest Physical Component Summary/Mental Component Summary scores (31.0/26.7) and physical and neurocognitive performance versus survivors in the other clusters ($P < .001$).

CONCLUSION Nearly 50% of survivors had moderate to high multisymptom burden, which was associated with sociodemographic, treatment factors, HRQOL, and functional outcomes.

J Clin Oncol 41:497-507. © 2022 by American Society of Clinical Oncology

ASSOCIATED CONTENT

See accompanying editorial on page 439

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on August 15, 2022 and published at ascopubs.org/journal/jco on September 27, 2022: DOI https://doi.org/10.1200/JCO.22.00361

INTRODUCTION

The overall 5-year survival rate for childhood cancer has reached 85% today.[1] However, therapies predispose survivors to various late effects, for example, physical performance deficits,[2] neurocognitive performance impairment,[3] poor mental health,[4] subsequent neoplasms,[5] chronic health conditions,[6,7] and premature death.[8] Therefore, most childhood cancer survivors experience poorer health-related quality of life (HRQOL) compared with norms or siblings.[9]

The onset of therapy-induced late effects is hallmarked by perceived symptoms. Our previous study found that symptom experiences are prevalent among adult survivors of childhood cancer.[10] Survivors reported pain (59%), abnormal sensation (34%), memory problems (27%), somatization (19%), pulmonary symptoms (18%), and cardiac symptoms (17%); 75% of survivors experienced symptoms from two or more domains.[10] The patterns of multisymptoms experienced by childhood cancer survivors, a concept known as *symptom clusters*, are still unclear. Investigating symptom clusters is clinically meaningful because symptoms co-occurring as clusters denote a pattern of symptom burden. When multisymptoms co-occur, the joint effect magnifies the impact of individual symptoms on HRQOL.[11-14]

CONTEXT

Key Objective

Investigating risk factors for the patterns of concurrent symptoms (ie, symptom clusters) and the association between symptom clusters and clinical outcomes is helpful for managing high-risk cancer survivors. This study distinguished clusters of multisymptoms among adult survivors of childhood cancer, evaluated detailed treatment and sociodemographic factors associated with individual symptom clusters, and tested associations of symptom clusters with self-reported health-related quality of life and clinically assessed physical and neurocognitive performance.

Knowledge Generated

Fifty percent of adult survivors of childhood cancer had a moderate to high burden of multisymptoms, which was associated with treatment and disadvantaged sociodemographic factors. Survivors in the highest symptom burden cluster had the poorest health-related quality of life and functional performance.

Relevance *(S.B. Wheeler)*

These data provide insights about the nature and correlates of the most burdensome symptom clusters observed in childhood cancer survivors, from which risk management strategies can be more appropriately tailored.*

*Relevance section written by *JCO* Associate Editor Stephanie B. Wheeler, PhD, MPH.

Prior cancer research in symptom clusters often focuses on patients with adult-onset cancer. Varying clusters of multisymptoms in numbers and patterns have been found, depending upon the types of cancer, assessment methods, and analytic techniques.[15] In breast cancer, for example, one study identified four patient subgroups having unique patterns of multisymptoms (low in all symptoms, high in all symptoms, low pain/high fatigue, and high pain),[16] and another study found four subgroups (low, mild, moderate, and high in all symptoms).[12]

Studies investigating symptom clusters in pediatric oncology largely focus on patients undergoing cancer therapy.[17-24] Only two studies focused on adult survivors of childhood cancer.[14,25] One study identified three symptom clusters (low, moderate, and high in all symptoms) on the basis of symptoms of pain, fatigue, sleep, and emotional distress.[14] Another study elucidated three clusters (all high, moderate physical/low psychologic symptoms, and high physical/moderate psychologic symptoms) through the Memorial Symptom Assessment Scale.[25] In these studies, survivors grouped into higher symptom burden clusters had significantly poorer HRQOL versus those grouped into lower burden clusters.[14] However, previous studies lacked data to evaluate therapy-related associations of risk for specific cluster membership. Additionally, they used self-reported HRQOL without outcomes from clinical evaluations (eg, physical or neurocognitive performance) to investigate the associations with symptom clusters.

The objective of the current study was to identify patterns of concurrent multisymptoms among adult survivors of childhood cancer. Specifically, we identified cluster membership for subgroups of survivors through a symptom inventory relevant to late effects of pediatric cancer, evaluated detailed treatment and sociodemographic factors associated with individual symptom clusters, and tested associations of symptom clusters with self-reported HRQOL and clinically assessed physical and neurocognitive performance.

METHODS

Study Sample

We included 3,085 adult survivors of childhood cancer enrolled in the St Jude Lifetime Cohort (SJLIFE), a retrospectively constructed cohort with prospective follow-up to evaluate health outcomes among survivors treated for childhood cancer at St Jude Children's Research Hospital (SJCRH). SJLIFE participants returned to SJCRH to complete comprehensive clinical assessments, including physical and neurocognitive performance evaluations, as previously described.[26,27] Survivors also self-reported sociodemographic, symptom, and HRQOL outcomes using a modular paper-and-pencil survey. Clinical information (eg, cancer diagnosis and specific therapy) was abstracted from medical records. Additionally, 602 adults without a history of childhood cancer were recruited to serve as controls for the SJLIFE study and used in the current analysis to compare prevalence of symptom domains to that reported by survivors.

Data Collection

This study is a secondary analysis of SJLIFE baseline data collected from individuals treated between 1962 and 2012. Participants eligible for analysis were age $\geq$ 18 years at the time of clinical assessment and had survived $\geq$ 10 years since childhood cancer diagnosis. We excluded survivors with severe neurocognitive impairment who required proxies for survey completion. Of 3,373 eligible participants, 288 who had the survey completed by proxies (n = 234) or unevaluable surveys (n = 54) were excluded, leaving 3,085 survivors for analysis (Appendix Fig A1, online only). The study protocol was approved by

SJCRH's Institutional Review Board, and all participants provided informed consent.

Measurement

Symptoms. Symptom assessment comprised 37 items embedded in the modular survey. These items were adapted from the Childhood Cancer Survivor Study[28] and reported in a previous SJLIFE publication.[10] Among these items, 19 were created by Childhood Cancer Survivor Study investigators (oncologists and patient-reported outcome scientists) and 18 were derived from the Brief Symptom Inventory-18.[29] These symptoms were used to assess risk-based toxicities as outlined in the Children's Oncology Group guidelines and have demonstrated sensitivity to treatment exposures.[30,31] The assessment inquired 10 symptom domains: sensation (eight items), motor/movement (four items), cardiac (three items), pulmonary (two items), pain (four items), fatigue (two items), nausea (one item), memory (one item), anxiety (six items), and depression (six items). Appendix Table A1 (online only) summarizes the content and measurement properties of the symptom measure. We used a checklist approach to classify the presence of a symptom domain for each cancer survivor. For each survivor, a symptom domain was classified as present if one or more items within the domain were reported as present. These 10 domains captured three symptom groups: physical (sensation, motor/movement, cardiac, and pulmonary domains), somatic (pain, fatigue, and nausea domains), and psychologic (memory, anxiety, and depression domains) symptoms.

Outcomes: HRQOL and physical and neurocognitive performance. HRQOL in the past four weeks was assessed using the Medical Outcomes Study Short Form-36. We focused on Physical Component Summary (PCS) and Mental Component Summary (MCS) derived from the eight domains of the Short Form-36. T-scores were calculated for PCS and MCS (mean = 50/standard deviation [SD] = 10), with higher scores indicating better HRQOL.

Participants completed the Physical Performance Test administered by certified examiners. The Physical Performance Test evaluated specific tasks (quantitative sensory, motor, endurance, and mobility) that simulate activities of daily living of varying degrees of difficulty. Participants were observed and timed as they wrote a brief sentence, simulated eating, lifted a book and put it on a shelf, put on and removed a jacket, picked up a penny, walked 50 feet, and turned around in place. T-scores were calculated (mean = 50/SD = 10) to represent the physical performance status, with higher scores indicating better outcomes.[32,33]

Participants completed standard neurocognitive batteries administered by certified examiners. Fifteen individual neurocognitive ability tests covered four domains including attention,[34-37] processing/psychomotor speed,[38] memory, and executive function problems.[34-39] For each domain, participants were classified as having impairment if they performed ≥ 2 SDs below the age-adjusted national normative data on each of the tests. The total number of nonimpaired domains was calculated to represent the global neurocognitive performance, ranging from zero to four, with a higher total number indicating better outcomes.

Diagnosis, treatment, and sociodemographic covariates. Cancer diagnoses were grouped into CNS tumors, leukemia, lymphoma, and other extracranial solid tumors. Treatment variables included the type and cumulative doses of specific chemotherapy, the location and cumulative doses of specific radiation therapy, and having undergone an invasive surgical procedure. We included treatment doses in the multivariate analysis if the dose information was significantly associated with symptom clusters in bivariable analysis; otherwise, treatment variables were treated as a binary characteristic. Sociodemographic variables included age at evaluation, sex, race/ethnicity, educational status, marital status, and health insurance coverage.

Statistical Analyses

Descriptive statistics included the distribution of diagnosis and treatment variables, sociodemographic information, and prevalence of symptom domains. On the basis of the prevalence of 10 symptom domains, latent class analysis identified subgroups of survivors who experienced similar patterns of symptom burden. Smaller Bayesian information criterion (BIC), smaller sample-size-adjusted BIC, significant Vuong-Lo-Mendell-Rubin likelihood ratio test ($P < .05$), and clinical interpretability as the primary criteria,[40] and higher entropy as the secondary criterion, were used to determine the optimal number of clusters.

Logistic regression compared the prevalence in symptom domains between survivors and controls, adjusting for age, sex, and race/ethnicity. Logistic regression examined associations of treatment and sociodemographic factors with symptom cluster membership, first fitting a series of bivariate models with a single factor as the covariate and then including all factors with a bivariate $P < .20$ in the multivariate models. Four separate multivariable linear and logistic regression models tested associations of symptom cluster membership with four outcomes of interest (ie, PCS, MCS, physical performance, and neurocognitive performance) adjusting for sociodemographic and treatment factors. F-tests compared differences in each outcome variable across symptom clusters. Statistical differences were identified by $P < .05$ (two-sided). All analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC) and Mplus 8.0.[41]

RESULTS

Participant Characteristics

Table 1 presents the characteristics of 3,085 participants. The mean age at evaluation was 32 years. Approximately 50% of survivors were male; more than 50% had been diagnosed with leukemia or lymphoma. Compared with

TABLE 1. Characteristics of Study Participants (n = 3,085)

Characteristic	Cancer Survivors
Age at evaluation, years, mean (SD; range)	31.9 (8.3; 18.1-63.3)
Time since cancer diagnosis, years, mean (SD; range)	28.1 (9.1; 11.0-54.0)
Sex, No. (%)	
Male	1,550 (50.3)
Female	1,531 (49.7)
Race/ethnicity, No. (%)	
White, non-Hispanic	2,370 (79.7)
Black, non-Hispanic	392 (13.2)
Hispanic	144 (4.8)
Other	68 (2.3)
Educational status, No. (%)	
Below HS	272 (8.9)
HS graduate/general educational development	594 (19.4)
Some college/training after HS	1,112 (36.4)
College graduate/postgraduate	1,081 (35.3)
Marital status, No. (%)	
Married	1,302 (42.9)
Unmarried (widowed, divorced, separated, or single)	1,731 (57.1)
Current employment status, No. (%)	
Employed (full-time/part-time)	2,036 (67.0)
Unemployed	1,004 (33.0)
Health insurance coverage, No. (%)	
Insured	2,428 (77.6)
Uninsured	700 (22.4)
Annual personal income, US dollars, No. (%)	
≤ $19,999	1,556 (52.6)
$20,000 to $59,999	1,089 (36.8)
≥ $60,000	315 (10.6)
Primary cancer diagnosis, No. (%)	
Leukemia	1,144 (37.1)
CNS tumors	298 (9.7)
Lymphoma	625 (20.3)
Solid tumors	1,018 (33.0)
Any chemotherapy, No. (%)	2,394 (77.6)
Bleomycin	157 (5.1)
Corticosteroids	1,254 (40.6)
Cytarabine	1,050 (34.0)
Methotrexate	1,466 (47.5)
Plant alkaloids	2,198 (71.2)
Platinum agents	367 (11.9)
Vincristine	2,094 (68.5)
Anthracycline, mg/m^2	
0	1,248 (40.5)
1-249	1,360 (44.1)
≥ 250	465 (15.1)
Alkylating agents, mg/m^2	
0	1,250 (40.5)
1-3,999	285 (9.2)
4,000-7,999	530 (17.2)
≥ 8,000	995 (32.3)
Any radiation therapy, No. (%)	1,791 (58.1)
Brain radiation, Gy	
0	2,062 (66.9)
1-17.9	169 (5.5)
18-29.9	585 (19.0)
≥ 30	268 (8.7)
Chest radiation	917 (29.7)
Abdominal-pelvic radiation	761 (24.7)
Invasive surgery, No. (%)	2,187 (70.9)

(continued in next column)

TABLE 1. Characteristics of Study Participants (n = 3,085) (continued)

Abbreviations: HS, high school; SD, standard deviation.

community controls, survivors were significantly younger in age at evaluation and included a higher proportion of male sex and non-Hispanic Black race/ethnicity ($P < .01$; Appendix Table A2, online only). Survivors had a significantly higher risk of experiencing all 10 symptom domains compared with controls (Appendix Table A3, online only). Some symptom domains were prevalent among controls, including up to 20% in sensation, depression, and anxiety, and 66% in pain.

Symptom Clusters on the Basis of 10 Symptom Domains

Restricted to the solutions of zero to six symptom clusters derived from the latent class analysis (Appendix Table A4, online only), the four-cluster model reflected symptom patterns that were clinically interpretable and statistically acceptable (the lowest BIC/sample-size-adjusted BIC, significant Vuong-Lo-Mendell-Rubin Likelihood Ratio test). Figure 1 presents the prevalence of survivors in the four symptom clusters: cluster 1 included survivors (n = 1,617; 52.4%) with low physical, somatic, and psychologic symptom burden; cluster 2 (n = 497; 16.1%) with high psychologic, moderate somatic, and low physical symptom burden; cluster 3 (n = 544; 17.6%) with high physical, moderate somatic, and low psychologic symptom burden; and cluster 4 (n = 427; 13.9%) with high physical, somatic,

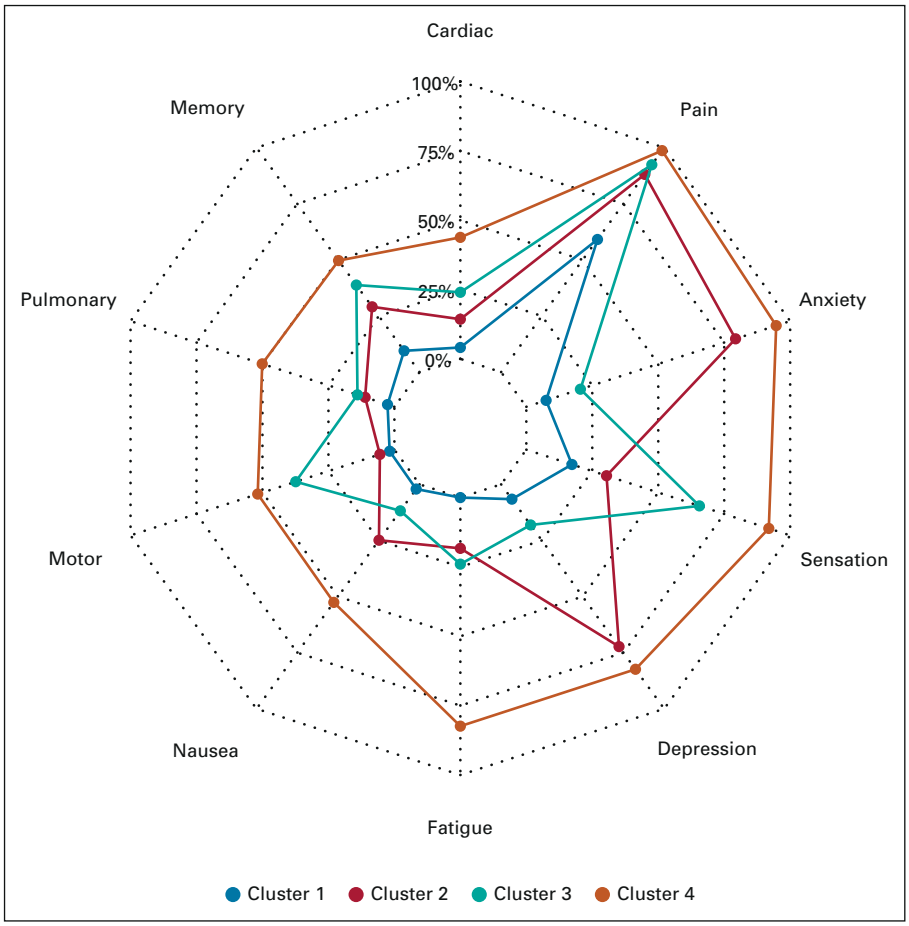

FIG 1. The cluster pattern of 10 symptom domains.[a,b] [a]Symptom cluster 1 = low physical, somatic, and psychologic symptoms; symptom cluster 2 = low physical, moderate somatic, and high psychologic symptoms; symptom cluster 3 = high physical, moderate somatic, and low psychologic symptoms; symptom cluster 4 = high physical, somatic, and psychologic symptoms. [b]Cluster size (%) in cluster 1: n = 1,617 (52.4%); cluster 2: n = 497 (16.1%); cluster 3: n = 544 (17.6%); cluster 4: n = 427 (13.9%).

and psychologic symptom burden. Pain was the most prevalent symptom domain in the four clusters.

Figure 2 presents a significant difference in prevalence of symptom clusters by four major diagnoses ($P < .05$). Compared with other diagnoses, a higher proportion of survivors treated for CNS tumors experienced high physical, moderate somatic, and low psychologic symptom burden (cluster 3).

Sociodemographic and Treatment Factors Associated With Specific Symptom Clusters

Table 2 presents sociodemographic and treatment factors associated with individual symptom clusters. Overall, stronger associations with risk factors were found among survivors classified to cluster 4 versus clusters 2 and 3 (all *v* cluster 1). Specifically, sociodemographic risk factors among survivors classified by symptom cluster 4 included older age at evaluation (odds ratio [OR], 1.08; 95% CI, 1.05 to 1.11), female sex (OR, 2.51; 95% CI, 1.85 to 3.41), less than high school education (OR, 7.71; 95% CI, 4.46 to 13.31), unmarried status (OR, 1.46; 95% CI, 1.05 to 2.05), and lack of health insurance (OR, 1.49; 95% CI, 1.04 to 2.13). Survivors treated with corticosteroids had a 1.76-fold elevated risk (95% CI, 1.02 to 3.03) of symptom cluster 4 membership (*v* cluster 1). For risk of symptom cluster 3 membership (*v* cluster 1), survivors who received platinum agents had a 2.22-fold increased risk (95% CI, 1.34 to 3.68) and survivors who were exposed to brain radiation ≥ 30 Gy had a 3.99-fold increased risk (95% CI, 2.33 to 6.86). However, no treatment factors were significantly associated with cluster 2 membership (*v* cluster 1).

Symptom Clusters Associated With Health Outcomes

Table 3 presents significant differences in HRQOL across four symptom clusters ($P < .001$). Survivors in symptom cluster 1 had the highest average scores on PCS (55.6) and MCS (54.1), whereas survivors in symptom cluster 4 had the lowest average PCS (31.0) and MCS (26.7), ≥ 2 SD

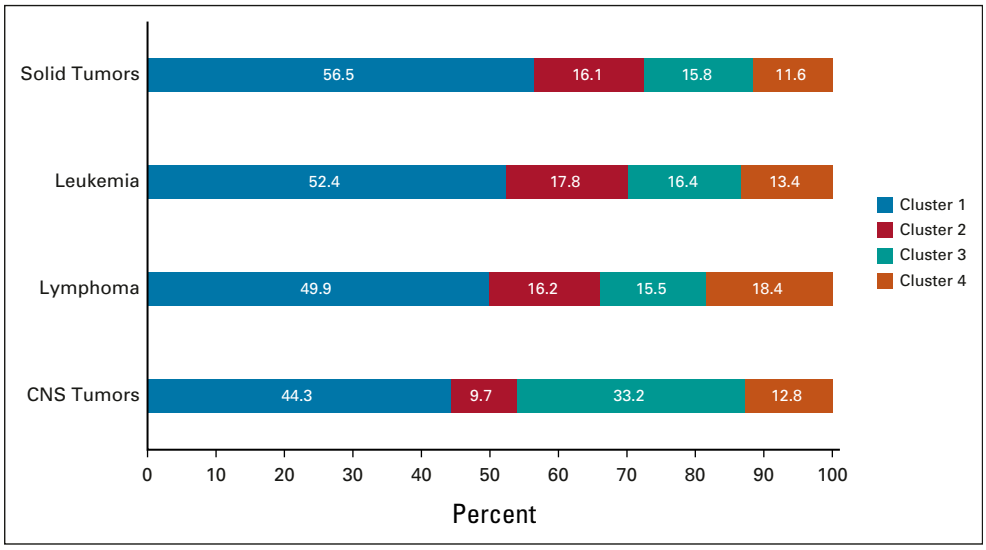

FIG 2. Prevalence of symptoms clusters[a] by four major cancer diagnosis groups. [a]Symptom cluster 1 = low physical, somatic, and psychologic symptoms; symptom cluster 2 = low physical, moderate somatic, and high psychologic symptoms; symptom cluster 3 = high physical, moderate somatic, and low psychologic symptoms; symptom cluster 4 = high physical, somatic, and psychologic symptoms.

below the norm. Survivors in symptom cluster 2 had average MCS scores of 38.6, ≥ 1 SD below the norm.

Table 3 also presents significant disparities in physical and neurocognitive performance across the four symptom clusters ($P < .001$). Survivors in cluster 1 had the best physical and neurocognitive performance, whereas survivors in cluster 3 or 4 had worse physical and neurocognitive performance.

Differential Associations of Treatment Factors and Health Outcomes by Symptom Clusters

Appendix Table A5 (online only) presents distinct associations of treatment factors with health outcomes among survivors experiencing different clusters of symptoms. Receipt of abdominal-pelvic radiation (*v* none) was associated with a significantly lower average PCS score by 4.43 points (95% CI, –8.16 to –0.71), and receipt of 4,000-7,999 mg/m^2 (*v* 0) alkylating agents was associated with a significantly lower average PCS score by 6.50 points (95% CI, –10.70 to –2.30) among survivors experiencing high physical, moderate somatic, and low psychologic symptom burden (cluster 3). Treatment with brain radiation 18 Gy (*v* 0) was associated with significantly lower physical performance by 7.32 points (95% CI, –10.94 to –3.71) among survivors within symptom cluster 3, and lower physical performance by 6.31 points (95% CI, –10.45 to –2.71) among survivors experiencing high physical, somatic, and psychologic symptom burden (cluster 4). Survivors treated with brain radiation ≥ 18 Gy (*v* 0) had significantly lower neurocognitive performance if they experienced cluster 3 or 4 symptoms ($P < .05$).

DISCUSSION

This is among the few studies evaluating symptom clusters for adult survivors of childhood cancer. We identified four distinct symptom clusters and associations with health outcomes. The results from the analyses of more than 3,000 clinically assessed childhood cancer survivors provide important insights that can inform future clinical management of this high-risk population. We found that at the mean age of 32 years, nearly 50% of childhood cancer survivors had moderate to high burden in physical, somatic, or psychologic symptom domains. Moreover, the prevalence of individual symptom clusters was found to be associated with specific treatment exposures and disadvantaged sociodemographic factors, with more severe burden of symptom clusters being associated with poorer HRQOL, and physical and neurocognitive outcomes.

Extant literature has well documented the effects of cancer treatment on adverse clinical outcomes among childhood cancer survivors, but evidence on symptom problems is sparse. For example, late effects related to receipt of platinum agents include hearing loss, renal dysfunction, metabolic syndrome, and peripheral sensory/motor neuropathy,[30,42] and organ injuries related to receipt of brain radiation include cranial nerve dysfunction, motor/sensory deficits, growth hormone deficiency, cerebrovascular complications, and low lean-muscle mass/weakness.[30,42] By including treatment data, we found that survivors being treated with platinum agents and ≥ 30 Gy brain radiation had an elevated risk for high physical, moderate somatic, and low psychologic symptom burden (cluster 3). A high proportion of brain tumor survivors experiencing cluster 3 symptoms (Fig 2) further support the significant associations between brain

TABLE 2. Multivariable Associations of Sociodemographic and Treatment Factors With Symptom Domains Classified by Four Symptom Clusters

	Symptom Cluster 2 *v* 1[a]		Symptom Cluster 3 *v* 1[a]		Symptom Cluster 4 *v* 1[a]	
Factor	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age at evaluation, years	0.98 (0.95 to 1.02)	.3250	1.07 (1.02 to 1.11)	< .0001	1.08 (1.05 to 1.11)	< .0001
Age at cancer diagnosis, years	1.01 (0.98 to 1.04)	.5050	0.99 (0.95 to 1.02)	.4680	0.99 (0.98 to 1.02)	.6150
Sex						
Male	Reference		Reference		Reference	
Female	2.32 (1.69 to 3.28)	< .0001	1.51 (1.06 to 2.15)	.0240	2.51 (1.85 to 3.41)	< .0001
Race/ethnicity						
White, non-Hispanic	Reference		Reference		Reference	
Others	1.13 (0.77 to 1.65)	.5340	1.40 (0.84 to 2.34)	.1960	1.24 (0.84 to 1.84)	.2690
Educational status						
Below HS	2.03 (1.07 to 3.85)	.0300	2.65 (1.39 to 5.04)	.0030	7.71 (4.46 to 13.31)	< .0001
HS graduate/GED	1.93 (1.21 to 3.09)	.0060	1.76 (1.05 to 2.94)	.0320	4.15 (2.65 to 6.52)	< .0001
Some college/training after HS	1.53 (1.04 to 2.25)	.0300	1.19 (0.76 to 1.86)	.4470	2.55 (1.69 to 3.85)	< .0001
College graduate/postgraduate	Reference		Reference		Reference	
Marital status						
Married	Reference		Reference		Reference	
Unmarried (widowed, divorced, separated, or single)	1.20 (0.85 to 2.70)	.2960	1.21 (0.81 to 1.80)	.3620	1.46 (1.05 to 2.05)	.0260
Health insurance coverage						
Uninsured	1.35 (0.93 to 1.96)	.1170	0.97 (0.61 to 1.54)	.8940	1.49 (1.04 to 2.13)	.0280
Insured	Reference		Reference		Reference	
Corticosteroids, yes/no	1.66 (0.92 to 3.00)	.0930	1.75 (0.90 to 3.41)	.1000	1.76 (1.02 to 3.03)	.0430
Methotrexate, yes/no	0.59 (0.31 to 1.09)	.0920	0.75 (0.36 to 1.56)	.4470	0.63 (0.36 to 1.11)	.1120
Platinum agents, yes/no	0.62 (0.33 to 1.17)	.1380	2.22 (1.34 to 3.68)	.0020	1.06 (0.62 to 1.80)	.8350
Anthracycline, mg/m^2						
0	Reference		Reference		Reference	
1-249	1.14 (0.74 to 1.77)	.5490	0.65 (0.39 to 1.09)	.1040	0.87 (0.58 to 1.31)	.5010
≥ 250	1.23 (0.72 to 2.10)	.4590	0.73 (0.41 to 1.28)	.2680	0.90 (0.55 to 1.45)	.6550
Alkylating agents, mg/m^2						
0	Reference		Reference		Reference	
1-3,999	1.26 (0.70 to 2.28)	.4450	1.37 (0.69 to 2.72)	.3760	1.34 (0.75 to 2.39)	.3290
4,000-7,999	1.21 (0.78 to 1.89)	.3910	0.86 (0.45 to 1.64)	.6500	1.38 (0.88 to 2.15)	.1570
≥ 8,000	1.11 (0.74 to 1.65)	.6220	1.56 (1.00 to 2.44)	.0530	1.33 (0.90 to 1.94)	.1490
Brain radiation, Gy						
0	Reference		Reference		Reference	
1-17.8	1.03 (0.49 to 2.16)	.9350	1.37 (0.62 to 3.03)	.4340	0.91 (0.43 to 1.90)	.8010
18-29.9	1.47 (0.92 to 2.33)	.1060	1.22 (0.66 to 2.25)	.5290	1.00 (0.60 to 1.65)	.9890
≥ 30	0.79 (0.33 to 1.87)	.5870	3.99 (2.33 to 6.86)	< .0001	1.61 (0.88 to 2.15)	.1230
Abdominal-pelvic radiation, yes/no	1.00 (0.66 to 1.52)	.9980	1.16 (0.77 to 1.75)	.4870	1.00 (0.68 to 1.47)	.9970

Abbreviations: GED, general education development; HS, high school; OR, odds ratio.

[a]Symptom cluster 1 = low physical, somatic, and psychologic symptoms; symptom cluster 2 = low physical, moderate somatic, and high psychologic symptoms; symptom cluster 3 = high physical, moderate somatic, and low psychologic symptoms; symptom cluster 4 = high physical, somatic, and psychologic symptoms.

TABLE 3. Differences in PCS, MCS, Physical Performance, and Neurocognitive Performance Outcomes Across Four Symptom Clusters[a]

	Overall		Symptom Cluster 1[b]		Symptom Cluster 2[b]		Symptom Cluster 3[b]		Symptom Cluster 4[b]		Comparisons Across Four Clusters	
Outcome	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**F-Statistic**	***P***
PCS[c]	50.61	0.18	55.58	0.17	53.93	0.18	41.89	1.37	30.98	1.13	292.19	< .001
MCS[c]	47.97	0.21	54.06	0.25	38.59	1.14	52.41	0.36	26.73	1.89	268.52	< .001
Physical performance[c]	50.00	0.19	52.60	0.23	51.59	0.53	45.05	0.85	46.06	0.79	61.53	< .001
Neurocognitive performance[c]	3.19	0.03	3.52	0.04	3.29	0.09	2.65	0.11	2.69	0.12	36.91	< .001

Abbreviations: MCS, Mental Component Summary; PCS, Physical Component Summary.

[a]Adjusting for covariates listed in Table 2 that were significantly associated with health-related quality of life, physical performance, and neurocognitive performance.

[b]Symptom cluster 1 = low physical, somatic, and psychologic symptoms; symptom cluster 2 = low physical, moderate somatic, and high psychologic symptoms; symptom cluster 3 = high physical, moderate somatic, and low psychologic symptoms; symptom cluster 4 = high physical, somatic, and psychologic symptoms.

[c]Higher scores for better health outcomes.

radiation exposure and cluster 3 symptoms (Table 2). Importantly, survivors treated with corticosteroids had an almost two-fold elevated risk for high burden in physical, somatic, and psychologic symptom domains (cluster 4). This finding suggests that some survivors are at risk for complex long-term symptom burden possibly associated with both neuropsychiatric (eg, insomnia, cognitive deficit, psychosis, and depression) and physical (eg, low bone mineral density, osteonecrosis, and metabolic syndrome) disorders resulting from corticosteroids treatment for pediatric cancer.[30,42,43]

In addition to therapy, various sociodemographic factors were significantly associated with symptom burden classified by clusters 2, 3, and 4. The stronger associations were observed in cluster 4 survivors who were more likely to have lower educational status and lack health insurance. In previous research, disadvantaged sociodemographic factors, rather than disease or treatment, predicted severe symptom profiles among patients with cancer.[44] In fact, cancer survivors with low educational status, low income, and no health insurance, especially among racial/ethnic minorities, often do not receive adequate follow-up care or share their survivorship care plan with clinicians.[45,46] Moreover, sociodemographically disadvantaged survivors often have a high symptom burden and poor awareness of symptoms associated with future health issues.[47-50] These compounding issues suggest the importance of screening for social determinants of symptom burden on a comprehensive scale throughout the cancer journey to advance health equity for childhood cancer survivors.

Previous research often correlated symptom clusters with functional outcomes using self-reported or provider-reported measures (eg, the European Organisation for Research and Treatment of Cancer-C30 and Karnofsky Performance Scale) that are subjective or subject to high interobserver variability.[51-53] We evaluated physical and neurocognitive performance using clinical batteries to reflect survivors' capability of performing daily activities. It is salient that survivors having high physical, somatic, and psychologic symptom burden (cluster 4) had remarkably poor physical and mental HRQOL. Interestingly, the patterns of symptom burden across the four clusters associated with physical and neurocognitive performance were similar (ie, best performance in cluster 1, followed by cluster 2, and equivalently lowest between clusters 3 and 4). We speculate there are common biological pathways underlying symptom clusters and physical and neurocognitive deficits in survivors.

There are distinct associations of treatment factors with health outcomes by individual symptom clusters. For example, survivors treated with brain radiation ≥ 18 Gy had significantly lower physical or neurocognitive performance if they experienced cluster 3 or 4 symptoms. This finding suggests that symptom clusters may be on the pathway for treatment effects on health outcomes, so the degree to which treatment factors associated with outcomes of interest may be modified by the patterns of multisymptoms. Future longitudinal studies are required to elucidate causal mechanisms. Practically, collecting meaningful symptom cluster data that can be integrated with treatment factors is an important consideration so that algorithms for risk-based management strategies could be designed to stratify subgroups of survivors who may benefit from specific interventions for symptom management. Assessing high-risk or alarm symptoms that raise concern for severe illness and require evaluation has been shown to be cost-effective for early diagnosis of adverse outcomes in different populations compared with asymptomatic surveillance.[54-60] With the high symptom burden experienced by survivors of childhood cancer, our findings support the importance of exploring the etiology of co-occurring symptoms, which may inform the design of effective interventions to address these symptoms.[61-63] Although pharmaceutical and nonpharmaceutical interventions targeting multisymptoms have been shown to improve symptom burden and HRQOL,[63-65] future research is needed to evaluate the effectiveness of interventions on symptom clusters in association with progression of clinical outcomes (functional performance, chronic

health conditions, and mortality) that map specific symptom profiles onto underlying health problems resulting from cancer treatments.

Several limitations should be noted. First, our results may not be generalizable to all childhood cancer survivors because participants were recruited from a single institution. Second, symptom clusters were identified using extant items from the SJLIFE survey and merely captured symptom presence rather than severity. Future research is essential to design comprehensive symptom measures (eg, the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events[66]) to measure a broader range of symptom domains, including severity, for childhood cancer survivors. Third, we focused on long-term adult survivors who received treatment more than three decades ago, despite still reflecting treatment exposures in clinical practice. Studies of survivors being treated with newer agents or modalities (eg, immunotherapy and targeted agents)[67] may identify different patterns of symptom clusters.

In conclusion, a substantial proportion of adult survivors of childhood cancer had a moderate to high burden of multisymptoms, which were associated with different sociodemographic and treatment factors. Survivors in the highest burden of symptom cluster had poorest HRQOL and functional performance. Future research is needed to elucidate factors underpinning symptom burden, including social determinants of health, and the longitudinal impact of symptom burden on long-term survivor health outcomes.

AFFILIATIONS

[1]College of Nursing, Ewha Womans University, Seoul, South Korea
[2]Department of Public Health Education, University of North Carolina Greensboro, Greensboro, NC
[3]Department of Global Pediatric Medicine, St Jude Children's Research Hospital, Memphis, TN
[4]Department of Oncology, St Jude Children's Research Hospital, Memphis, TN
[5]Department of Epidemiology and Cancer Control, St Jude Children's Research Hospital, Memphis, TN
[6]Capstone College of Nursing, University of Alabama, Tuscaloosa, AL
[7]Department of Biostatistics, St Jude Children's Research Hospital, Memphis, TN
[8]Department of Psychology, St Jude Children's Research Hospital, Memphis, TN

CORRESPONDING AUTHOR

I-Chan Huang, PhD, Department of Epidemiology and Cancer Control, St Jude Children's Research Hospital, 262 Danny Thomas Place, MS735, Memphis, TN 38105; e-mail: i-chan.huang@stjude.org.

DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

PRIOR PRESENTATION

Presented at the 2021 ASCO annual meeting, virtual, June 4-8, 2021 (abstr 10046).

SUPPORT

Supported by the National Cancer Institute under award numbers U01CA195547 (Primary PI: M.M.H.; Multiple PIs: K.K.N. and L.L.R.), R01CA238368 (Primary PI: I.-C.H.; Multiple PI: J.N.B.), R01CA258193 (Primary PI: I.-C.H.; Multiple PI: Y.Y.), and T32CA225590 (Primary PI: K.R.K.).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.00361.

AUTHOR CONTRIBUTIONS

Conception and design: Hyewon Shin, William N. Dudley, T. Robin Bartlett, Deokumar Srivastava, Leslie L. Robison, Kevin R. Krull, Melissa M. Hudson, I-Chan Huang
Financial support: Yutaka Yasui, Justin N. Baker, Leslie L. Robison, Kirsten K. Ness, Kevin R. Krull, Melissa M. Hudson, I-Chan Huang
Administrative support: Kirsten K. Ness, Kevin R. Krull, Melissa M. Hudson
Provision of study materials or patients: Leslie L. Robison, Kirsten K. Ness, Melissa M. Hudson
Collection and assembly of data: Madeline R. Horan, Leslie L. Robison, Kirsten K. Ness, Kevin R. Krull, I-Chan Huang
Data analysis and interpretation: Hyewon Shin, William N. Dudley, Nickhill Bhakta, Zhaoming Wang, Deokumar Srivastava, Yutaka Yasui, Justin N. Baker, Kirsten K. Ness, Kevin R. Krull, Melissa M. Hudson, I-Chan Huang
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors would like to thank Debra C. Wallace, PhD, RN, and Heidi Krowchuk, PhD, RN, both from School of Nursing, University of North Carolina at Greensboro, for input on the initial design of this study.

REFERENCES

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2019. CA Cancer J Clin 69:7-34, 2019
2. Ness KK, Hudson MM, Ginsberg JP, et al: Physical performance limitations in the Childhood Cancer Survivor Study Cohort. J Clin Oncol 27:2382-2389, 2009
3. Krull KR, Hardy KK, Kahalley LS, et al: Neurocognitive outcomes and interventions in long-term survivors of childhood cancer. J Clin Oncol 36:2181-2189, 2018
4. Brinkman TM, Recklitis CJ, Michel G, et al: Psychological symptoms, social outcomes, socioeconomic attainment, and health behaviors among survivors of childhood cancer: Current state of the literature. J Clin Oncol 36:2190-2197, 2018
5. Friedman DL, Whitton J, Leisenring W, et al: Subsequent neoplasms in 5-year survivors of childhood cancer: The Childhood Cancer Survivor Study. J Natl Cancer Inst 102:1083-1095, 2010

6. Bhakta N, Liu Q, Ness KK, et al: The cumulative burden of surviving childhood cancer: An initial report from the St Jude Lifetime Cohort Study (SJLIFE). Lancet 390:2569-2582, 2017
7. Hudson MM, Ness KK, Gurney JG, et al: Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA 309:2371-2381, 2013
8. Armstrong GT, Chen Y, Yasui Y, et al: Reduction in late mortality among 5-year survivors of childhood cancer. N Engl J Med 374:833-842, 2016
9. Zeltzer LK, Lu Q, Leisenring W, et al: Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: A report from the Childhood Cancer Survivor Study. Cancer Epidemiol Biomark Prev 17:435-446, 2008
10. Huang IC, Brinkman TM, Kenzik K, et al: Association between the prevalence of symptoms and health-related quality of life in adult survivors of childhood cancer: A report from the St Jude Lifetime Cohort Study. J Clin Oncol 31:4242-4251, 2013
11. Miaskowski C, Aouizerat BE, Dodd M, et al: Conceptual issues in symptom clusters research and their implications for quality-of-life assessment in patients with cancer. JNCI Monogr 2007:39-46, 2007
12. Dodd MJ, Cho MH, Cooper BA, et al: The effect of symptom clusters on functional status and quality of life in women with breast cancer. Eur J Oncol Nurs 14: 101-110, 2010
13. Astrup GL, Hofsø K, Bjordal K, et al: Patient factors and quality of life outcomes differ among four subgroups of oncology patients based on symptom occurrence. Acta Oncol 56:462-470, 2017
14. Finnegan L, Campbell RT, Ferrans CE, et al: Symptom cluster experience profiles in adult survivors of childhood cancers. J Pain Symptom Manage 38:258-269, 2009
15. Dong ST, Butow PN, Costa DSJ, et al: Symptom clusters in patients with advanced cancer: A systematic review of observational studies. J Pain Symptom Manage 48:411-450, 2014
16. Kim HJ, Barsevick AM, Beck SL, et al: Clinical subgroups of a psychoneurologic symptom cluster in women receiving treatment for breast cancer: A secondary analysis. Oncol Nurs Forum 39:E20-E30, 2012
17. Baggott C, Cooper BA, Marina N, et al: Symptom cluster analyses based on symptom occurrence and severity ratings among pediatric oncology patients during myelosuppressive chemotherapy. Cancer Nurs 35:19-28, 2012
18. Hockenberry MJ, Hooke MC, Gregurich M, et al: Symptom clusters in children and adolescents receiving cisplatin, doxorubicin, or ifosfamide. Oncol Nurs Forum 37:E16-E27, 2010
19. Wang J, Jacobs S, Dewalt DA, et al: A longitudinal study of PROMIS pediatric symptom clusters in children undergoing chemotherapy. J Pain Symptom Manage 55:359-367, 2018
20. Li R, Ma J, Chan Y, et al: Symptom clusters and influencing factors in children with acute leukemia during chemotherapy. Cancer Nurs 43:411-418, 2020
21. Hooke MC, Hatch D, Hockenberry MJ, et al: The longitudinal parallel process analysis of biomarkers of oxidative stress, symptom clusters, and cognitive function in children with leukemia. J Pediatr Oncol Nurs 37:244-254, 2020
22. Hooke MC, Mathiason MA, Blommer A, et al: Symptom clusters, physical activity, and quality of life: A latent class analysis of children during maintenance therapy for leukemia. Cancer Nurs 45:113-119, 2022
23. Williamson Lewis R, Effinger KE, Wasilewski-Masker K, et al: Self-reported late effect symptom clusters among young pediatric cancer survivors. Support Care Cancer 29:8077-8087, 2021
24. Li R, Yao W, Chan Y, et al: Correlation between symptom clusters and quality of life in children with acute leukemia during chemotherapy. Cancer Nurs 45: 96-104, 2022
25. Hong HC, Kim YM, Min A: Symptom clusters in childhood cancer survivors in Korea: A latent class analysis. Eur J Cancer Care (Engl) 29:e13322, 2020
26. 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 56:825-836, 2011
27. Howell CR, Bjornard KL, Ness KK, et al: Cohort profile: The St. Jude Lifetime Cohort Study (SJLIFE) for paediatric cancer survivors. Int J Epidemiol 50:39-49, 2021
28. Robison LL, Armstrong GT, Boice JD, et al: The Childhood Cancer Survivor Study: A National Cancer Institute-supported resource for outcome and intervention research. J Clin Oncol 27:2308-2318, 2009
29. Derogatis L: Brief Symptom Inventory 18: Administration, Scoring, and Procedures Manual. Minneapolis, MN, National Computer Systems, 2000
30. Hudson MM, Bhatia S, Casillas J, et al: Long-term follow-up care for childhood, adolescent, and young adult cancer survivors. Pediatrics 148:e2021053127, 2021
31. Landier W, Bhatia S, Eshelman DA, et al: Development of risk-based guidelines for pediatric cancer survivors: The Children's Oncology Group long-term follow-up Guidelines from the Children's Oncology Group late effects Committee and Nursing Discipline. J Clin Oncol 22:4979-4990, 2004
32. Reuben DB, Siu AL: An objective measure of physical function of elderly outpatients. The Physical Performance Test. J Am Geriatr Soc 38:1105-1112, 1990
33. Smith WA, Li Z, Loftin M, et al: Measured versus self-reported physical function in adult survivors of childhood cancer. Med Sci Sports Exerc 46:211-218, 2014
34. Conners C: Conners' Continuous Performance Test II (CPT II). North Tonawanda, NY, Multi-Health Systems, 2001
35. Conners C: Conners' Continuous Performance Test (CPT 3) and Conners' Continuous Auditory Test of Attention (CATA) (ed 3). North Tonawanda, NY, Multi-Health Systems, 2014
36. Reitan R: The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation (ed 2). Tucson, AZ, Neuropsychology Press, 1993
37. Tombaugh T, Rees L, McIntyre N: Normative Data for the Trail Making Test (ed 2). New York, NY, Oxford University Press, 1996
38. Wechsler D: Wechsler Adult Intelligence Scale (ed 4). San Antonio, TX, Psychological Corporation, 2008
39. Delis D, Kaplan E, Kramer J: Delis-Kaplan Executive Function System. San Antonio, TX, Psychological Corporation, 2001
40. Sinha P, Calfee CS, Delucchi KL: Practitioner's guide to latent class analysis: Methodological considerations and common pitfalls. Crit Care Med 49:e63-e79, 2021
41. Muthén L, Muthén B: Mplus User's Guide (ed 8). Los Andeles, CA, Muthén & Muthén, 1998-2017
42. Dixon SB, Bjornard KL, Alberts NM, et al: Factors influencing risk-based care of the childhood cancer survivor in the 21st century. CA Cancer J Clin 68:133-152, 2018
43. Ismail MF, Lavelle C, Cassidy EM: Steroid-induced mental disorders in cancer patients: A systematic review. Future Oncol 13:2719-2731, 2017
44. Miaskowski C, Cooper BA, Melisko M, et al: Disease and treatment characteristics do not predict symptom occurrence profiles in oncology outpatients receiving chemotherapy. Cancer 120:2371-2378, 2014
45. Palmer NRA, Weaver KE, Hauser SP, et al: Disparities in barriers to follow-up care between African American and White breast cancer survivors. Support Care Cancer 23:3201-3209, 2015

46. Dimartino LD, Birken SA, Mayer DK: The relationship between cancer survivors' socioeconomic status and reports of follow-up care discussions with providers. J Cancer Educ 32:749-755, 2017
47. Woods LM, Rachet B, Coleman MP: Origins of socio-economic inequalities in cancer survival: A review. Ann Oncol 17:5-19, 2006
48. Aktas A, Walsh D, Rybicki L: Symptom clusters and prognosis in advanced cancer. Support Care Cancer 20:2837-2843, 2012
49. Xiao C: The state of science in the study of cancer symptom clusters. Eur J Oncol Nurs 14:417-434, 2010
50. Niksic M, Rachet B, Duffy SW, et al: Is cancer survival associated with cancer symptom awareness and barriers to seeking medical help in England? An ecological study. Br J Cancer 115:876-886, 2016
51. Laird BJA, Scott AC, Colvin LA, et al: Pain, depression, and fatigue as a symptom cluster in advanced cancer. J Pain Symptom Manage 42:1-11, 2011
52. Dodd MJ, Cho MH, Cooper BA, et al: Identification of latent classes in patients who are receiving biotherapy based on symptom experience and its effect on functional status and quality of life. Oncol Nurs Forum 38:33-42, 2011
53. Ji Y-B, Bo C-L, Xue X-J, et al: Association of inflammatory cytokines with the symptom cluster of pain, fatigue, depression, and sleep disturbance in Chinese patients with cancer. J Pain Symptom Manage 54:843-852, 2017
54. Forster AS, Renzi C, Lyratzopoulos G: Diagnosing cancer in patients with "non-alarm" symptoms: Learning from diagnostic care innovations in Denmark. Cancer Epidemiol 54:101-103, 2018
55. Jensen H, Torring ML, Olesen F, et al: Cancer suspicion in general practice, urgent referral and time to diagnosis: A population-based GP survey and registry study. BMC Cancer 14:636, 2014
56. Neal RD, Din NU, Hamilton W, et al: Comparison of cancer diagnostic intervals before and after implementation of NICE guidelines: Analysis of data from the UK General Practice Research Database. Br J Cancer 110:584-592, 2014
57. Neal RD, Tharmanathan P, France B, et al: Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. Br J Cancer 112:S92-S107, 2015 (suppl 1)
58. Redaniel MT, Martin RM, Ridd MJ, et al: Diagnostic intervals and its association with breast, prostate, lung and colorectal cancer survival in England: Historical cohort study using the Clinical Practice Research Datalink. PLoS One 10:e0126608, 2015
59. Mendonca SC, Abel GA, Lyratzopoulos G: Pre-referral GP consultations in patients subsequently diagnosed with rarer cancers: A study of patient-reported data. Br J Gen Pract 66:e171-e181, 2016
60. Dahl TL, Vedsted P, Jensen H: The effect of standardised cancer pathways on Danish cancer patients' dissatisfaction with waiting time. Dan Med J 64:A5322, 2017
61. Zhou X, Menche J, Barabási A-L, et al: Human symptoms–disease network. Nat Commun 5:4212, 2014
62. Dodd MJ, Miaskowski C, Paul SM: Symptom clusters and their effect on the functional status of patients with cancer. Oncol Nurs Forum 28:465-470, 2001
63. Miaskowski C, Barsevick A, Berger A, et al: Advancing symptom science through symptom cluster research: Expert panel proceedings and recommendations. J Natl Cancer Inst 109:djw253, 2017
64. Berger AM, Yennu S, Million R: Update on interventions focused on symptom clusters: What has been tried and what have we learned? Curr Opin Support Palliat Care 7:60-66, 2013
65. Kwekkeboom KL: Cancer Symptom cluster management. Semin Oncol Nurs 32:373-382, 2016
66. Basch E, Reeve BB, Mitchell SA, et al: Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 106:dju244, 2014
67. Dixon SB, Chow EJ, Hjorth L, et al: The future of childhood cancer survivorship: Challenges and opportunities for continued progress. Pediatr Clin North Am 67: 1237-1251, 2020
68. Kline RB: Principles and Practice of Structural EquationModeling (ed 4). New York, NY, The Guilford Press, 2015

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Associations of Symptom Clusters and Health Outcomes in Adult Survivors of Childhood Cancer: A Report From the St Jude Lifetime Cohort Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

William N. Dudley
Consulting or Advisory Role: Carevive (Inst)

Deokumar Srivastava
Consulting or Advisory Role: General Dynamics Information Technology

Kevin R. Krull
Patents, Royalties, Other Intellectual Property: Royalties from Wolters Kluwer

Melissa M. Hudson
Consulting or Advisory Role: Oncology Research Information Exchange Network, Princess Máxima Center

No other potential conflicts of interest were reported.

APPENDIX

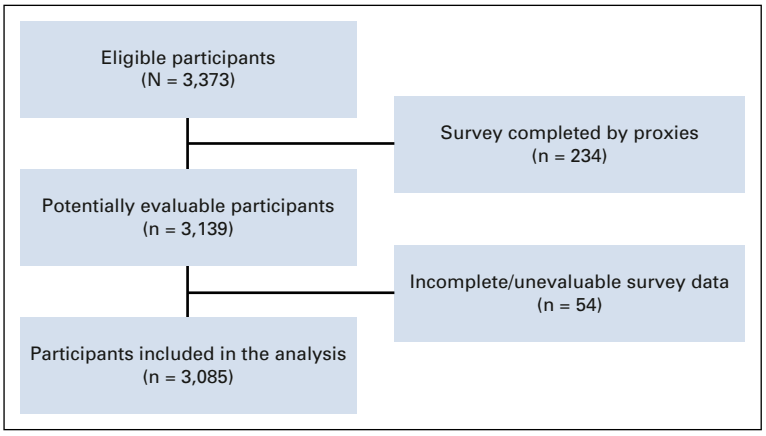

FIG A1. The process of recruiting study participants (adult survivors of childhood cancer).

TABLE A1. A List of Symptom Items and Corresponding Symptom Domains

		Fit Indices[a,b]		
Domain	**Items**	**RMSEA**	**CFI**	**SRMR**
Cardiac symptoms	Irregular heartbeat/palpitation Angina pectoris Shortness of breath or irregular heartbeat when exercising	0.00	1.00	0.00
Pulmonary symptoms	Chronic cough Trouble getting breath	0.00	1.00	0.00
Sensation abnormalities	Decreased sense of touch Tinnitus/ringing in ear Dizziness/vertigo Double vision Trouble seeing when wearing glasses Very dry eyes Abnormal sense of taste Numbness	0.06	0.82	0.04
Motor symptoms	Balance equilibrium problems Tremors Weakness to move arm Weakness to move leg	0.08	0.97	0.03
Nausea	Nausea	NA	NA	NA
Pain	Migraine Severe headaches Prolonged pain in arms, legs, or back Pain in general	0.08	0.70	0.06
Fatigue	Faintness Feeling weak	0.00	1.00	0.00
Memory problems	Memory problems	NA	NA	NA
Anxiety	Suicidal thought Feeling lonely Feeling blue Feeling no interest in things Feeling hopeless about the future Feeling of worthless	0.09	0.95	0.04
Depression	Nervousness Suddenly scared for no reasons Feeling fearful Feeling tense Spells of terror Restless cannot sit still	0.10	0.94	0.04

Abbreviations: CFI, Comparative Fit Index; RMSEA, Root Mean Square Error of Approximation; SRMR, Standardized Root Mean Squared Error.

[a]Performance of each multi-item symptom domain was tested using confirmatory factor analysis. There is a consensus on using different fit indices, especially CFI, RMSEA, and SRMR, to evaluate the performance of multi-item measures (see Kline[68]). The suggested criteria for the acceptable performance of multi-item measures include RMSEA $\leq$ 0.8, CFI $\geq$ 0.9, and SRMR $\leq$ 0.08.

[b]In this study, all multi-item symptom domains achieve the acceptable criteria on at least two fit indices.

TABLE A2. Differences in Age at Evaluation, Sex, Race/Ethnicity, and Educational Status Between Survivors and Controls

Characteristic	Survivors	Community Controls	*P*
Age at evaluation, years,[a] mean (SD; range)	31.9 (8.3; 18.1-63.3)	33.6 (10.3; 18.2-70.0)	< .001
Sex,[b] No. (%)			.002
Male	1,550 (50.3)	259 (43.2)	
Female	1,531 (49.7)	341 (56.8)	
Race/ethnicity,[b] No. (%)			< .001
White, non-Hispanic	2,370 (79.7)	485 (80.6)	
Black, non-Hispanic	392 (13.2)	35 (5.8)	
Hispanic	144 (4.8)	42 (7.0)	
Other	68 (2.3)	40 (6.6)	
Educational status,[b] No. (%)			< .001
Below HS	272 (8.9)	17 (3.0)	
HS graduate/general educational development	594 (19.4)	70 (12.4)	
Some college/training after HS	1,112 (36.4)	175 (30.9)	
College graduate/postgraduate	1,081 (35.3)	305 (53.8)	

Abbreviations: HS, high school; SD, standard deviation.
[a]Student's *t*-test.
[b]Chi-squared test.

TABLE A3. Prevalence of Symptom Domains Between Cancer Survivors and Community Controls

Symptom Domain	Survivors Prevalence, %	Community Controls Prevalence, %	Survivors *v* Community Controls[a]	
			OR (95% CI)[b]	*P*
Cardiac	14.0	7.5	2.37 (1.71 to 3.27)	< .001
Pulmonary	12.4	6.1	2.44 (1.72 to 3.46)	< .001
Sensation	35.3	16.9	3.19 (2.54 to 4.02)	< .001
Motor	17.5	4.0	5.49 (3.61 to 8.34)	< .001
Nausea	14.5	10.1	1.64 (1.23 to 2.18)	.001
Pain	73.7	66.1	1.72 (1.42 to 2.09)	< .001
Fatigue	18.2	7.6	3.16 (2.29 to 4.35)	< .001
Memory	27.5	7.9	4.44 (3.27 to 6.04)	< .001
Anxiety	32.7	21.2	1.99 (1.61 to 2.46)	< .001
Depression	29.8	18.7	1.92 (1.54 to 2.39)	< .001

Abbreviation: OR, odds ratio.
[a]N = 602 noncancer individuals who serve as the control group of the St Jude Lifetime Cohort Study. Eligible community controls were age ≥ 18 years at the time of participation; non–first-degree relatives or friends of St Jude patients, or any volunteer not associated with St Jude; and not treated for childhood cancer.
[b]Adjusting for age at assessment, sex, and race/ethnicity.

TABLE A4. Fit Indices Across Different Latent Class Models

No. of Symptom Clusters Identified	BIC	Sample Size Adjusted BIC	VLMR-LRT, *P*	Entropy
1	31,517.77	31,485.99	—	0.780
2	28,167.42	28,100.70	0.0000	0.696
3	27,888.76	27,787.08	0.0000	0.678
4	27,719.19	27,582.56	0.0000	0.704
5	27,737.05	27,565.47	0.2400	0.716
6	28,227.59	28,021.05	0.1573	0.780

Abbreviations: BIC, Bayesian Information Criterion; VLMR-LRT, Vuong-Lo-Mendell-Rubin likelihood ratio test.

TABLE A5. Multivariable Associations of Treatment Factors With PCS, Physical Performance, and Neurocognitive Performance Outcomes Stratified by Symptom Clusters (only listing treatment factors significantly associated with health outcomes)[a]

		PCS[c,d]		Physical Performance[c]		Neurocognitive Performance[c]	
Treatment Factors	**Symptom Cluster[b]**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Platinum agents							
Yes *v* no	Cluster 1	–1.16*	–2.13 to –0.18				
Anthracycline, mg/m^2							
≥ 250 *v* 0	Cluster 1	–1.43*	–2.48 to –0.37				
Abdominal-pelvic radiation							
Yes *v* no	Cluster 1	–0.93**	–1.56 to –0.31				
Yes *v* no	Cluster 3	–4.43**	–8.16 to –0.71				
Alkylating agents, mg/m^2							
4,000-7,999 *v* 0	Cluster 3	–6.50**	–10.70 to –2.30				
Brain radiation, Gy							
≥ 18 *v* 0	Cluster 3			–7.32**	–10.94 to –3.71	–0.91***	–1.36 to –0.47
≥ 18 *v* 0	Cluster 4			–6.31**	–10.45 to –2.17	–0.59*	–1.19 to –0.00

Abbreviations: MCS, Mental Component Summary; PCS, Physical Component Summary.

*$P < .05$

**$P < .01$

***$P < .001$

[a]Adjusting for covariates listed in Table 2 that were significantly associated with health-related quality of life, physical performance, and neurocognitive performance.

[b]Symptom cluster 1 = low physical, somatic, and psychologic symptoms; symptom cluster 3 = high physical, moderate somatic, and low psychologic symptoms; symptom cluster 4 = high physical, somatic, and psychologic symptoms.

[c]Higher scores for better health outcomes.

[d]Treatment factors were not significantly associated with MCS after stratifying symptom clusters; therefore, MCS was not included in this table.