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Comorbid Symptoms of Emotional Distress in Adult Survivors of Childhood Cancer

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Abstract

Background—Childhood cancer survivors are at risk for emotional distress symptoms, but symptom comorbidity has not been previously examined. We examined distress profiles in adult survivors of childhood cancer diagnosed between 1970 and 1999.

Methods—Self-reported depression, anxiety, and somatization symptoms from the Brief Symptom Inventory-18 were examined in survivors (N=16,079) and siblings (N=3,085) from the Childhood Cancer Survivor Study. Latent profile analysis identified clusters of survivors with individual and comorbid symptoms. Disease, treatment and demographic predictors of distress comorbidity patterns were examined using multinomial logistic regressions.

Results—Four clinically relevant profiles were identified: low distress on all subscales (asymptomatic, 62%); high distress on all subscales (comorbid distress, 11%); elevated somatization (somatic symptoms, 13%); elevated depression and anxiety (affective distress, 14%). Compared to siblings, fewer survivors were asymptomatic (62% *v.* 74%, p<0.0001) and more had comorbid distress (11% *v.* 5%, p<0.0001). Survivors of leukemia (OR 1.34, 95%CI 1.12–1.61), CNS tumor (OR 1.30, 95%CI 1.05–1.61), and sarcoma (OR 1.26, 95%CI 1.01–1.57) had higher comorbid distress risk than solid tumor survivors. Psychoactive medications were associated with comorbid distress (p's< 0.0001), suggesting this group was refractory to traditional medical management. Comorbid distress was associated with poor perceived health (OR 31.7, 95%CI 23.1–43.3); headaches (OR 3.2, 95%CI 2.8–3.7) and bodily pain (OR 4.0, 95%CI 3.2–5.0).

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All authors made substantial contributions to the study concept, design, data analyses, interpretation of results, and manuscript.

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Conclusion—A significant proportion of survivors are at risk for comorbid distress, which may require extensive treatment approaches beyond those utilized for individual symptoms.

Abbreviated abstract

We examined emotional distress profiles in childhood cancer survivors. We identified four unique patterns, including a group with comorbid symptoms that require different intervention approaches.

Keywords

Comorbidity; Quality of life; Psychosocial late effect; Brief Symptom Inventory-18; Latent profile analysis

Pediatric cancer survival has improved, leading to growing numbers of adult survivors of childhood cancer[1] at risk for physical, neurocognitive, and psychosocial late effects of their disease and treatment.[2–4] Monitoring emotional distress in long-term childhood cancer survivors is recommended standard of care across North America and Europe.[5–8]

Cross-sectional studies of emotional distress have shown that although most survivors are well-adjusted,[9,10] some experience significant distress.[10,11] Prevalence rates of post-traumatic stress in survivors have been reported to be as high as 35%.[12,13] Survivors report higher levels of distress compared to siblings[10,14] and non-cancer psychotherapy patients,[14] and are twice as likely to report suicidal ideation compared to siblings.[15,16] Longitudinal studies of depression, anxiety and somatization symptoms, measured with the Brief Symptom Inventory (BSI-18),[17] indicate that most survivors report consistently low distress levels, but, importantly, a subset report persistently elevated or increasing distress over time.[9]

The BSI-18 is used in clinical groups and the general population; its three-factor structure (depression, anxiety, somatization) was confirmed in childhood cancer survivors.[18] Previous studies examined BSI subscales separately, or used the Global Severity Index (GSI: sum of the three subscales) to measure overall distress. However, elevations on one or more subscales result in elevated GSI scores for different symptom combinations. Thus distress profiles cannot be appreciated by the GSI or each subscale alone. Profiling comorbid symptoms is necessary to develop effective, personalized interventions, particularly for those most in need. Different interventions target combined depression-anxiety versus somatic symptoms. Survivors with complex or comorbid distress may be refractory to routine clinical care, requiring intense, multimodal treatments. To address these needs, examining single scores is insufficient; an approach that measures single symptoms and symptom clusters is needed to profile survivors for targeted interventions.

The aims of this study were to identify clusters of survivors based on combined distress symptoms using latent profile analysis (LPA), and to determine disease, treatment, and sociodemographic predictors associated with each cluster. We hypothesized the following clusters based on a conceptual distinction between physical (somatic) and affective (anxiety and depression) symptoms: (1) low scores on all three BSI-18 subscales (asymptomatic), (2)

high scores on all three subscales (comorbid emotional distress), (3) primarily somatization (somatic symptoms), (4) primarily depression and/or anxiety (affective distress).

METHODS

Population

The Childhood Cancer Survivor Study (CCSS) is a multi-institutional retrospective cohort study, with longitudinal follow-up of childhood cancer survivors treated at 31 institutions in North America (https://ccss.stjude.org/). Survivors (n=16,079) in this analysis were diagnosed with cancer (leukemia, central nervous system (CNS) malignancy, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue sarcoma, bone tumor) before age 21, treated between January 1, 1970 and December 31, 1999 and alive five years after diagnosis.. Their siblings (n=3085) served as a comparison group. Respondents were at least 18 years old and completed the BSI-18 on their baseline evaluation (1992–2015). The CCSS methodology and design have been previously described,[19] approved by institutional review boards at all sites, and participants provided informed consent.

Measures

Emotional distress was measured using the BSI-18. Depression, anxiety, and somatization subscale scores were converted to T-scores (mean 50, SD 10) based on community normative data.[17] Predictors of distress included primary cancer diagnosis, age at diagnosis, time since diagnosis, current perceived health, pain, chemotherapy, radiation, and sociodemographic variables including sex, race, age, health insurance, education, marital status and annual household income. Psychoactive medications were classified based on the American Hospital Formulary Service Drug Information database as previously described.[22]

Data Analyses

T-tests and chi-square tests were used to compare demographic characteristics between survivors and siblings. LPA was used to identify sibling clusters based on BSI-18 symptom patterns. Latent clusters were first identified in siblings by randomly splitting the cohort into training (50%) and validation sets (50%). For the training set, LPA was run with a pre-specified number of latent clusters, K, ranging from 2 to 6. Akaike information criterion, Bayesian information criterion, and Lo-Mendell-Rubin adjusted likelihood ratio tests were used to determine K. At least 5% of the sample was required to include each cluster. Adjusted rand index was used to measure reliability between clusters identified by LPA in the validation set and by nearest centroid method to validate the training set cluster model. The centers of the validated cluster model in siblings were used to derive latent clusters in survivors using nearest centroid method. Derived clusters from this approach were used for all analyses in survivors. To verify that siblings and survivors had the same cluster pattern, LPA was run in survivors using the same training and validation process as that in siblings. Frequencies and percentages of cluster membership were compared between survivors and siblings using chi-square tests. Frequencies across clusters were examined by diagnosis, diagnosis decade, treatment, and individual variables associated with emotional distress,[9–11,22–24] and comparisons made using chi-square tests for categorical and analyses

of variance for continuous variables. Separate multinomial regressions were generated for diagnosis and treatment predictors, and for predictors associated with long-term outcomes of diagnosis/treatment (e.g. educational attainment, perceived current health, pain). Risk for comorbid, somatic or affective cluster membership was referenced to the asymptomatic cluster. No adjustments were made for multiple comparisons.

RESULTS

Survivor and sibling demographics, and survivor diagnosis and treatment characteristics are presented in Table 1.

Comorbidity Patterns

LPA supported a 4-cluster model for siblings and survivors (Supplemental Table 1). Good agreement between training and validation clusters (Adjusted Rand Index; siblings = 0.78, survivors = 0.88) was demonstrated. Cluster membership frequency differed between groups (χ^2 = 204.5, p<0.0001), with more siblings than survivors in the asymptomatic cluster (sibling n=2294, 74.4% vs survivor n=9914, 61.8%, p<.0001). In contrast, more survivors than siblings were in the comorbid (survivor n=1722, 10.7% vs sibling n=149, 4.8%; p<0.0001), somatic (survivor n=2168, 13.5% vs sibling n= 281, 9.1%; p<0.0001) and affective clusters (survivor n=2229, 13.9% vs sibling n=361, 11.7%; p=0.0011). Moreover, survivors and siblings within the comorbid cluster had scores above the clinical cutoff (T≥63) on all three scales, while those in affective or somatic clusters were primarily impaired on depression or somatization scales, respectively (Table 2). Frequency of survivor cluster membership differed by demographic, diagnosis, treatment and health-related predictors (Table 3). From the 1970's to the 1990's rates of affective distress in survivors declined, but comorbid distress increased (χ^2=16.9; p=0.0095). All classes of psychoactive medication use were associated with comorbid distress (all p's <0.0001).

Comorbidity Predictors

In the diagnosis multivariable model (Table 4), CNS tumor survivors were at approximately 30% higher risk of comorbid symptoms (OR 1.30, 95%CI 1.05–1.61) and affective distress (OR 1.29, 95%CI 1.08–1.55) compared to solid tumor survivors. Other diagnoses associated with comorbid distress included leukemia (OR 1.34, 95%CI 1.12–1.61) and bone and soft tissue sarcomas (OR 1.26, 95%CI 1.01–1.57).

In the treatment multivariable model (Table 5), cranial radiation was associated with a 14% higher risk of affective distress (OR 1.14, 95%CI 1.01–1.28) compared to no radiation. Radiation to other parts of the body was associated with a 27% higher risk of somatic symptoms (OR 1.27, 95%CI 1.12–1.44). Alkylating agents were associated with affective distress (OR 1.16, 95%CI 1.04–1.30). In contrast, anthracyclines reduced the risk of affective distress (OR 0.72, 95%CI 0.64–0.81) and steroids reduced the likelihood of somatic symptoms by 17% (OR 0.83, 95%CI 0.73–0.94).

The health-related predictor multivariable model (Table 6) included variables potentially affected by diagnoses/ treatments. We therefore excluded diagnosis/treatment variables to avoid confounding. Compared to survivors reporting excellent perceived health, those with

fair/poor health had a 32-fold risk for comorbid distress (OR 31.66, 95%CI 23.13–43.34), a 9-fold risk for somatic symptoms (OR 8.97, 95%CI 7.17–11.23), and a 6-fold risk for affective distress (OR 5.59, 95%CI 4.48–6.97). Survivors with headache and bodily pain showed similar patterns. Divorced/separated marital status, less than college education, and lower income were risks for comorbid distress. Having health insurance decreased risk of distress cluster membership, suggesting higher untreated distress in those uninsured. In terms of race, black survivors were less likely than white survivors to have comorbid or affective distress. In all 3 models, female sex was a risk for somatic symptoms and comorbid distress.

DISCUSSION

Profiling patterns of distress in long-term childhood cancer survivors revealed novel findings including identification of four distinct groups: those who were asymptomatic, those with affective distress, those with somatic symptoms and, most importantly, a significant proportion with comorbid distress. Frequencies of affective, somatic, and comorbid symptoms were higher in survivors than in siblings. Among survivors, 38% demonstrated a pattern of distress, with affective distress and somatic symptoms being most common. Moreover, 11% were categorized in the comorbid distress cluster, more than twice the rate in siblings. Our approach highlights unique cluster membership predictors, implications for at-risk patient identification, and targeted intervention development.

Comorbid distress was associated with CNS tumor, leukemia, and sarcoma diagnoses, and poor perceived health, headache, and bodily pain. Other comorbid distress predictors included female sex, low income and marital status (single, divorced/separated). Survivors in the comorbid distress cluster reported the highest distress levels on all three subscales. Along with the asymptomatic group, survivors in the comorbid distress cluster had the highest rates of psychoactive medication use. Psychoactive medications may therefore be effective in alleviating symptoms in asymptomatic survivors. Those in the comorbid group remain symptomatic because they may be resistant to treatment or not managed adequately. These findings raise concerns because previous work showed that survivors tend to under-report social and/or emotional difficulties[25] and that BSI-18 scores may underestimate distress in adult childhood cancer survivors.[26] Those studies raise the possibility that the frequency and level of distress – particularly comorbid distress – may be underestimated in this study.

The current analysis supports a distinction between affective distress and somatic symptoms, with survivors who received cranial radiation at increased risk for affective distress, and those who received non-cranial radiation at increased risk for somatic symptoms. Predictors of affective distress also included treatment with alkylating agents, younger age at diagnosis, and shorter time since diagnosis. In contrast, steroid or anthracycline treatments were protective for somatic symptoms. Together, this suggests that brain injury due to diagnosis or treatment poses a significant risk for depression or comorbid distress, consistent with evidence of depression many years after childhood traumatic brain injury.[27]

Although diagnosis, treatment, age and time variables contributed to distress comorbidities, the odds ratios were relatively small, consistent with research suggesting that cancer treatment variables account for a small proportion of the variance when measuring distress in long-term survivors.Critical variables underlying survivors' long-term distress and psychological adaptation include cognitive factors such as coping style,[28,29] perceptions about the cancer experience,[30] perceived health[9] and/or current physical health..

Sociodemographic factors that mitigate comorbid distress include college education, high income, living as married, and medical insurance coverage. Higher socioeconomic status and/or increased access to support services contribute to better psychological outcomes in diverse patient groups including cancer.[11,31] With the advent of the Affordable Care Act, it will be interesting to explore longitudinal changes in distress and utilization of support services in American survivors.

Limitations of this work include reliance on self-reported outcomes, absence of information regarding psychiatric history, other stressful life events, or psychosocial variables that contribute to distress. However, emotional distress inherently depends on mental state self-evaluation, therefore self-report is often the most accurate way to assess symptoms. Important follow-up analyses include examining persistence of identified distress patterns and changes in health status associated with longitudinal comorbid distress.

Notwithstanding these limitations, this study provides novel information on distress comorbidity profiles. Risk factors identified in our study are similar to those identified in previous reports of elevations of single BSI-18 subscales. However, those studies do not distinguish between survivors elevated on multiple scales and survivors who are not. By profiling symptom clusters, we identify groups of survivors based on different symptomatology patterns and associated risk, with implications for implementing specific interventions based on cluster profile. Multimodal interventions are likely necessary to address complex profiles reported by comorbid distress cluster members, including psychoactive medications, and psychotherapy exploring survivors' attitudes towards their cancer experience. Survivors endorsing primarily somatic symptoms may need pharmacological and strategic management of symptoms and chronic pain, including mindfulness or physical exercise. Those in the affective distress cluster may benefit most from antidepressant and cognitive behavioral treatments. Our findings lay the groundwork for clinical trials that evaluate effectiveness of treatments based on distress symptom profiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and treatment characteristics

	Survivors (N=16079)		Siblings (N=3085)		p-value
	N	%	N	%	
Sex					
Male	8323	51.8	1437	46.6	<0.0001
Female	7756	48.2	1648	53.4	
Race					
White	14070	87.5	2835	91.9	<0.0001
Black	976	6.1	76	2.5	
Other	923	5.7	174	5.6	
Ethnicity					
Hispanic	1187	7.4	105	3.4	<0.0001
Non-Hispanic	14816	92.2	2980	96.6	
Age					
18–24	6169	38.4	881	28.6	<0.0001
25–29	4582	28.5	720	23.3	
30–34	3298	20.5	675	21.9	
≥35	2030	12.6	809	26.2	
Education					
<High school	1212	7.5	163	5.3	<0.0001
High school	3110	19.3	547	17.7	
Some college	5688	35.4	1083	35.1	
≥College graduate	5495	34.2	1165	37.8	
Marital Status					
Single	7955	49.5	994	32.2	<0.0001
Married/Live as married	6413	39.9	1740	56.4	
Divorced/separated	1275	7.9	297	9.6	
Household Income					

	Survivors (N=16079)		Siblings (N=3085)		p-value
	N	%	N	%	
≤19,999	2224	13.8	215	7.0	<0.0001
20,000–39,999	2810	17.5	416	13.5	
40,000–59,999	2725	17.0	497	16.1	
60,000–79,999	2082	13.0	484	15.7	
≥80,000	3996	24.8	1188	38.5	
Insurance					
Yes	13163	81.9	2721	88.2	<0.0001
No	2657	16.5	333	10.8	
Perceived Health Status					
Excellent	2949	18.3	742	24.0	<0.0001
Very good	5932	36.9	1341	43.5	
Good	5128	31.9	811	26.3	
Fair/Poor	1950	12.1	163	5.3	
Pain					
Headache	4533	28.2	741	24.0	<0.0001
Other pain	906	5.6	96	3.1	
No pain	10164	63.2	2242	72.7	
Diagnosis					
Leukemia	4410	27.4			
CNS Tumor	2662	16.6			
Hodgkin lymphoma	2605	16.2			
Non-Hodgkin lymphoma	1597	9.9			
Kidney (Wilms)	1163	7.2			
Neuroblastoma	756	4.7			
Soft tissue sarcoma	1217	7.6			
Bone cancer	1669	10.4			
Treatment Era					
1970–1979	5501	34.2			

	Survivors (N=16079)		Siblings (N=3085)		p-value
	N	%	N	%	
1980–1989	5310	33.0			
1990–1999	5267	32.8			
Cancer Treatment					
Antimetabolites					
Yes	6045	37.6			
No	8449	52.6			
Anthracyclines					
Yes	6693	41.6			
No	7631	47.5			
Alkylating Agents					
Yes	7174	44.6			
No	6669	41.5			
Steroids					
Yes	6877	42.8			
No	7828	48.7			
Radiation					
None	6056	37.7			
Non-cranial	5786	36.0			
Cranial	2503	15.6			
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	
Age at baseline	27.1(5.9)	26 (18–48)	29.6 (7.3)	29 (18–56)	<0.0001
Age at Diagnosis	9.4(5.6)	10 (0–20)			
Time since diagnosis	17.7(4.3)	17.7 (6.4–31.1)			

Note. p-values based on Chi-square tests for categorical and two-sample t-tests for continuous variables; Frequencies based on number of participants for whom information was available; SD = standard deviation

Table 2

BSI subscale scores for survivors and siblings, by cluster.

Cluster	BSI subscale	Survivors			Siblings		
		Mean	SD	N impaired (%)	Mean	SD	N impaired (%)
Asymptomatic	Somatization	43.4	3.3	0 (0.0)	43.6	3.3	0 (0.0)
	Anxiety	41.3	4.6	8 (0.1)	42.8	5.8	8 (0.35)
	Depression	42.8	3.0	0 (0.0)	42.9	3.1	0 (0.0)
Somatic	Somatization	57.8	5.8	515 (23.8)	59.0	3.9	55 (19.6)
	Anxiety	49.3	7.7	82 (3.8)	49.2	8.5	15 (5.3)
	Depression	45.7	4.6	1 (0.05)	44.8	3.9	0 (0.0)
Affective	Somatization	46.7	5.0	2 (0.09)	46.0	4.5	0 (0.0)
	Anxiety	50.4	7.7	125 (5.6)	51.5	8.2	31 (8.6)
	Depression	60.2	5.2	586 (26.3)	60.9	4.0	104 (28.8)
Comorbid	Somatization	62.2	6.7	893 (51.9)	61.8	5.2	74 (49.7)
	Anxiety	63.1	7.8	857 (49.8)	61.5	7.5	61 (40.9)
	Depression	65.6	6.9	1073 (62.3)	65.6	6.4	89 (59.7)

Note. N impaired: number of cluster members with scores above the clinical cutoff (T ≥ 63).

Table 3

Frequency distributions for the four distress clusters in survivors

	Asymptomatic		Affective		Somatic		Comorbid		
	n	%	n	%	n	%	n	%	p-value*
Total	9914	61.6	2229	13.9	2168	13.5	1722	10.7	
Sex									
Male	5461	65.8	1199	14.5	866	10.4	770	9.3	<0.0001
Female	4453	57.6	1030	13.3	1302	16.8	952	12.3	
Race									
White	8687	61.9	1972	14.1	1885	13.4	1485	10.6	0.0005
Black	618	63.6	107	11.0	156	16.0	91	9.4	
Other	549	59.5	131	14.2	113	12.3	129	14.0	
Education									
<High school	598	49.7	202	16.8	189	15.7	214	17.8	<0.0001
High school	1930	62.2	388	12.5	405	13.1	378	12.2	
Some college	3411	60.1	812	14.3	764	13.5	685	12.1	
≥College graduate	3653	66.6	733	13.4	730	13.3	372	6.8	
Marital Status									
Single	4897	61.8	1300	16.4	904	11.4	826	10.4	<0.0001
Married/Live as married	4165	65	654	10.2	1022	16	562	8.8	
Divorced/separated	629	49.5	220	17.3	163	12.8	259	20.4	
Household Income									
≤19,999	1067	48.2	364	16.4	342	15.4	441	19.9	<0.0001
20,000–39,999	1641	58.5	415	14.8	408	14.5	341	12.2	
40,000–59,999	1670	61.4	380	14.0	386	14.2	283	10.4	
60,000–79,999	1355	65.2	281	13.5	284	13.7	159	7.6	
≥80,000	2749	69	495	12.4	474	11.9	268	6.7	
Perceived Health Status									
Excellent	2433	82.7	258	8.8	187	6.4	65	2.2	<0.0001
Very good	4138	69.9	811	13.7	645	10.9	323	5.5	

	Asymptomatic		Affective		Somatic		Comorbid		p-value*
	n	%	n	%	n	%	n	%	
Good	2725	53.3	845	16.5	865	16.9	680	13.3	
Fair/Poor	551	28.4	303	15.6	449	23.2	636	32.8	
Pain									
Headache	2049	45.3	682	15.1	923	20.4	869	19.2	<0.0001
Other pain	356	39.6	138	15.4	220	24.5	185	20.6	
No pain	7239	71.4	1338	13.2	958	9.4	603	5.9	
Psychoactive Medication									
Analgesics									
Yes	759	40.9	289	15.6	399	21.5	411	22.1	<0.0001
No	9155	64.6	1940	13.7	1769	12.5	1311	9.2	
Antidepressants									
Yes	442	31.4	283	20.1	240	17.1	442	31.4	<0.0001
No	9472	64.8	1946	13.3	1928	13.2	1280	8.8	
Anxiolytics, hypnotics, sedatives									
Yes	199	28.8	98	14.2	156	22.5	239	34.5	<0.0001
No	9715	63.3	2131	13.9	2012	13.1	1483	9.7	
CNS Stimulants									
Yes	106	43.3	43	17.6	40	16.3	56	22.9	<0.0001
No	9808	62.1	2186	13.8	2128	13.5	1666	10.6	
Neuroleptics									
Yes	79	27.7	45	15.8	61	21.4	100	35.1	<0.0001
No	9835	62.5	2184	13.9	2107	13.4	1622	10.3	
Muscle Relaxants									
Yes	107	33.6	39	12.3	79	24.8	93	29.2	<0.0001
No	9807	62.4	2190	13.9	2089	13.3	1629	10.4	
Diagnosis									
Leukemia	2723	62.0	622	14.2	542	12.3	506	11.5	0.0021
CNS tumor	1614	60.9	412	15.5	328	12.4	298	11.2	

	Asymptomatic		Affective		Somatic		Comorbid		p-value*
	n	%	n	%	n	%	n	%	
Hodgkin lymphoma	1594	61.3	341	13.1	396	15.2	270	10.4	
non-Hodgkin lymphoma	1013	63.6	219	13.7	204	12.8	158	9.9	
Kidney (Wilms)	737	63.5	148	12.8	164	14.1	111	9.6	
Neuroblastoma	472	62.5	105	13.9	116	15.4	62	8.2	
Soft tissue sarcoma	765	63.1	164	13.5	162	13.4	121	10	
Bone cancer	996	59.8	218	13.1	256	15.4	196	11.8	
Diagnosis Decade									
1970–79	3322	60.7	817	14.9	744	13.6	593	10.8	0.0095
1980–89	3306	62.4	753	14.2	700	13.2	538	10.2	
1990–99	3286	62.5	659	12.5	723	13.7	591	11.2	
Cancer Treatment									
Antimetabolites									
Yes	3669	60.9	857	14.2	798	13.2	700	11.6	0.1092
No	5168	61.3	1181	14.0	1191	14.1	887	10.5	
Anthracyclines									
Yes	4142	62.0	830	12.4	928	13.9	776	11.6	<0.0001
No	4607	60.6	1182	15.5	1033	13.6	783	10.3	
Alkylating Agents									
Yes	4369	61.0	1003	14.0	990	13.8	796	11.1	0.4790
No	4120	62.0	941	14.2	874	13.2	707	10.6	
Steroids									
Yes	4172	60.9	990	14.4	901	13.1	791	11.5	0.0485
No	4800	61.5	1085	13.9	1107	14.2	815	10.4	
Radiation									
None	3807	63.0	813	13.5	772	12.8	650	10.8	<0.0001
Non-cranial	2622	60.0	595	13.6	682	15.6	474	10.8	
Cranial	2332	60.1	612	15.8	491	12.7	446	11.5	
Age and Time									

	Asymptomatic		Affective		Somatic		Comorbid		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p-value***
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p-value
Age at baseline	27.1	5.9	26.5	5.8	27.6	6.0	27.3	5.9	<0.0001
Age at diagnosis	9.4	5.6	9.0	5.4	9.8	5.7	9.5	5.4	0.0001
Time since diagnosis	17.7	4.3	17.5	4.3	17.8	4.3	17.8	4.4	0.0633

Note. p-values based on chi-square tests for categorical and ANOVA for continuous variables; SD=standard deviation; Frequencies based on number of participants for whom information was available.

Table 4

Multivariable models predicting survivor distress cluster membership: diagnosis and sociodemographic factors

Risk Factor	Comorbid		Somatic		Affective	
	OR	95%CI	OR	95%CI	OR	95%CI
Diagnosis						
Solid tumors	1.0		1.0		1.0	
Bone and soft tissue sarcomas	**1.26**	**1.01–1.57**	0.99	0.82–1.20	1.15	0.95–1.40
CNS tumors	**1.30**	**1.05–1.61**	0.88	0.73–1.06	**1.29**	**1.08–1.55**
Leukemia	**1.34**	**1.12–1.61**	0.88	0.75–1.03	1.04	0.88–1.22
Lymphomas	1.16	0.93–1.44	0.97	0.80–1.16	1.17	0.97–1.41
Age at diagnosis (per year)	1.01	0.99–1.02	**1.02**	**1.01–1.03**	**0.98**	**0.97–0.99**
Time since diagnosis (per year)	1.01	0.99–1.02	**1.01**	**1.00–1.02**	**0.98**	**0.97–0.99**

Note. Solid tumors include Wilms tumor and neuroblastoma. Adjusted for sex and race. Risk for comorbid, somatic and affective cluster membership referenced to the asymptomatic cluster. OR associated with age at diagnosis based on each year older, and time since diagnosis based on each year from diagnosis.

Table 5

Multivariable models predicting survivor distress cluster membership: treatment and sociodemographic factors

Risk Factor	Comorbid		Somatic		Affective	
	OR	95%CI	OR	95%CI	OR	95%CI
Radiation						
None	1.0		1.0		1.0	
Radiation (Cranial vs. none)	1.06	0.93–1.20	1.07	0.95–1.21	**1.14**	**1.01–1.28**
Radiation (Noncranial vs. none)	1.00	0.87–1.16	**1.27**	**1.12–1.44**	1.11	0.97–1.26
Chemotherapy						
Antimetabolites (yes vs. no)	1.02	0.88–1.19	**1.19**	**1.03–1.37**	1.04	0.90–1.20
Anthracycline (yes vs. no)	1.08	0.95–1.23	0.96	0.85–1.09	**0.72**	**0.64–0.81**
Alkylating agents (yes vs. no)	0.99	0.88–1.12	1.10	0.98–1.23	**1.16**	**1.04–1.30**
Steroids (yes vs. no)	1.10	0.96–1.26	**0.83**	**0.73–0.94**	1.02	0.89–1.15
Age at diagnosis (per year)	1.00	0.99–1.01	**1.01**	**1.00–1.02**	0.98	0.97–0.99
Time since diagnosis (per year)	1.00	0.99–1.02	**1.01**	**1.00–1.02**	0.98	0.97–0.99

Note. Adjusted for sex and race. Risk for comorbid, somatic and affective cluster membership referenced to asymptomatic cluster. OR associated with age at diagnosis based on each year older, and time since diagnosis based on each year from diagnosis.

Table 6

Multivariable models predicting survivor cluster membership: socioeconomic, perceived health, pain, and sociodemographic factors

Risk Factor	Comorbid		Somatic		Affective	
	OR	95%CI	OR	95%CI	OR	95%CI
Education						
≥College graduate	1.0		1.0		1.0	
Some college	**1.51**	**1.29–1.76**	1.06	0.93–1.20	0.98	0.87–1.11
High school	1.17	0.97–1.42	0.90	0.77–1.06	0.76	0.65–0.89
<High school	**1.28**	**1.00–1.65**	1.18	0.94–1.47	1.22	0.99–1.51
Marital Status						
Married/living as married	1.0		1.0		1.0	
Divorced/separated/widowed	**2.61**	**2.13–3.20**	0.95	0.77–1.18	**2.24**	**1.85–2.72**
Single never married	**1.43**	**1.23–1.65**	**0.86**	**0.76–0.97**	**1.85**	**1.63–2.10**
Income						
≥80,000	1.0		1.0		1.0	
60,000–79,000	0.90	0.73–1.13	1.11	0.94–1.31	1.12	0.95–1.32
40,000–59,999	1.18	0.98–1.43	1.15	0.99–1.35	**1.21**	**1.04–1.41**
20,000–39,000	1.14	0.94–1.37	1.11	0.95–1.30	1.11	0.95–1.29
<20,000	**1.60**	**1.32–1.95**	1.16	0.97–1.39	**1.23**	**1.04–1.46**
Insurance (yes vs. no)	**0.62**	**0.53–0.72**	**0.82**	**0.70–0.95**	**0.70**	**0.60–0.80**
Perceived Health						
Excellent	1.0		1.0		1.0	
Very good	**2.78**	**2.05–3.77**	**1.90**	**1.57–2.29**	**1.87**	**1.58–2.21**
Good	**8.42**	**6.28–11.29**	**3.63**	**3.01–4.38**	**2.97**	**2.51–3.51**
Fair/poor	**31.66**	**23.13–43.34**	**8.97**	**7.17–11.23**	**5.59**	**4.48–6.97**
Pain						
No pain	1.0		1.0		1.0	
Headache	**3.24**	**2.84–3.70**	**2.53**	**2.25–2.84**	**1.53**	**1.36–1.73**
Bodily pain	**3.95**	**3.15–4.96**	**3.97**	**3.26–4.83**	**1.92**	**1.54–2.40**
Sex (female vs. male)	**1.20**	**1.06–1.37**	**1.47**	**1.32–1.64**	1.04	0.94–1.16

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Risk Factor	Comorbid		Somatic		Affective	
	OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Race						
White	1.0		1.0		1.0	
Black	**0.46**	**0.35–0.62**	0.94	0.75–1.17	**0.58**	**0.45–0.74**
Other	1.03	0.81–1.31	0.98	0.78–1.23	0.81	0.65–1.02
Age	0.99	0.98–1.01	0.99	0.98–1.00	1.00	0.99–1.01

Note. Risk for comorbid, somatic and affective cluster membership referenced to asymptomatic cluster. OR associated with age based on each year older.