Longitudinal Patterns and Predictors of Psychiatric Comorbidities and Pain in Survivors of Childhood Cancer

CCSS Working Groups: Psychology; Chronic Disease

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Background

Advances in treatment and supportive care have led to an impressive 5-year survival rate of over 80%[1–3], however, survivors face increased risk for psychological distress and pain in addition to other adverse health outcomes[4–6]. Previous studies have found the prevalence of general psychological distress, anxiety, and depression in adult survivors of childhood cancer has a wide range. A recent review and meta-analysis had a pooled prevalence estimates for general psychological distress of 32% of survivors, whereas pooled estimates for depression and anxiety were 29% and 24%, respectively[7]. Reports from the Childhood Cancer Survivor Study (CCSS) have identified several specific predictors of psychological distress, including female sex, neurotoxic treatment exposures, unemployment, single marital status, neurocognitive impairment, and pain[4,8–11]. Additionally, Brinkman et al.[12] identified four longitudinal patterns of distress in the original CCSS cohort: 1) few to no symptoms across time, 2) persistently elevated symptoms across time, 3) increasing symptoms across time, and 4) decreasing symptoms across time. Each pattern, or trajectory, had unique predictors. Increasing cancer-related pain was the strongest predictor of persistent and increasing distress symptoms. Furthermore, survivors with pain or chronic health conditions were significantly less likely to have decreasing symptoms or distress. Importantly, this study considered distress symptoms individually (i.e., separate longitudinal models for anxiety, depression, somatization) and did not examine how these symptoms occur together over time.

There are shared biological and environmental risk factors for depression and anxiety both in the general population and childhood cancer survivors. Pain is one of the most common predictors of elevated psychiatric symptoms in childhood cancer survivors and is consistently associated with anxiety and depression in the general population [13–15]. In addition, the associations between pain, depression, and anxiety are bidirectional, where they have been found to predict the onset of each other[13–17]. There is a similarly complex relationship between psychological distress and chronic health conditions. Studies have found that the likelihood of having psychological distress is three times higher in those living with chronic medical conditions[18]. A dose-response relationship was also identified for individuals with multiple chronic health conditions, where those with three or more health conditions had the highest likelihood of having psychological distress or worsened mental health, though all individuals with any number of chronic health conditions had higher odds of having psychological distress compared to those without a chronic health condition[19,20].

The relationship between anxiety and depression is also complicated. In the general population, they are highly comorbid[21–24] and even share somatic diagnostic criteria in the most recent edition of the Diagnostic and Statistical Manual[25], however, their temporal sequence is difficult to pinpoint[26,27]. Interestingly, the risk of developing an anxiety disorder is lower in individuals with depression; whereas the risk of developing depression is higher in individuals with anxiety disorders[21]. Additionally, anxiety is more likely to begin earlier

in development, during preadolescence and early adolescence, compared to depression, which often begins to emerge in late adolescence and early to mid-adulthood[28]. Among childhood cancer survivors, similar patterns of comorbidity have been identified. A previous report from CCSS identified four cross-sectional patterns of emotional distress symptoms: 1) low distress symptoms (62%); 2) high distress (elevated comorbid anxiety, depression, somatization, 11%); 3) affective distress (elevated anxiety and depression, 14%); 4) somatic distress (elevated somatization, 13%)[29].

While there is ongoing work to better understand the complex relationships between psychiatric symptoms and pain in the general population, there is limited research in childhood cancer survivors. Therefore, this study aims to build on past CCSS studies to characterize longitudinal patterns of comorbid psychiatric symptoms and pain and their relationship with other health conditions and functional outcomes. After identifying patterns of psychological comorbidity over time using the BSI-18, we will examine the relationships between those patterns with burden of chronic health conditions and a range of functional outcomes, including socioeconomic status, personal income, education, maintaining a job, and the ability to live independently.

Specific Aims

Aim 1: Identify longitudinal profiles of comorbid psychiatric symptoms and pain across three timepoints

Hypothesis 1.1: We will identify distinct longitudinal profiles of comorbid depression, anxiety, somatization, and pain in survivors

Aim 2: Identify demographic, diagnosis, and treatment-related predictors of longitudinal profiles of psychiatric symptoms and pain

Hypothesis 2.1: Female survivors will be more likely to be assigned to a latent profile characterized by persistent or increased comorbid psychiatric symptoms and pain compared to male survivors.
Hypothesis 2.2: Sociodemographic factors at baseline that indicate a lower socioeconomic status, including personal income, education, area deprivation index, and social vulnerability index, will be associated with profiles characterized by persistently elevated and increasing psychiatric symptoms and pain comorbidity

Aim 3: Identify chronic health conditions associated with different longitudinal profiles of psychiatric symptoms and pain

Hypothesis 3.1: Survivors with higher burden of chronic disease at baseline are more likely to be associated with a latent profile characterized by persistently elevated and increasing psychiatric symptoms and pain comorbidity.
Hypothesis 3.2: Survivors with an increasing chronic health condition burden over time are more likely to be associated with a latent profile characterized by persistently elevated and increasing psychiatric symptoms and pain comorbidity.

Exploratory Aim: Examine the bidirectional relationship between different longitudinal profiles of psychiatric symptoms and pain with chronic health conditions.

Aim 4: Identify functional limitations associated with different profiles of psychiatric comorbidity and pain

Hypothesis 4.1: Survivors assigned to profiles characterized by elevated or increased psychiatric symptoms and pain comorbidity will be more likely to have reduced functional outcomes (e.g., non-independent living, assistance with routine/personal care needs).

Methods

Study Population

We will include participants in CCSS over 18 years of age at baseline, who have self-completed the baseline survey and at least two follow-up surveys. For the original cohort, this will include baseline, FU2, and FU4. For the expansion cohort, this will include baseline, FU5, and FU7. We estimate there are approximately 10,000 participants with available data for all 3 time points across the original and expansion cohorts (see Table 2).

Outcome Variables

The primary outcome is the Brief Symptom Inventory – 18 (BSI-18) to assess global psychological distress, depression, anxiety, and somatization. We will use the continuous T-Scores for each symptom dimension. We will use the short-form health survey 36 (SF-36) to assess pain and pain interference.

Sociodemographic and Clinical Variables

- Sex
- Age at diagnosis
- Age at baseline
- Cancer diagnosis
    - Leukemia
    - CNS Tumor
    - Wilms Tumor
    - Lymphoma
    - Non-Hodgkin's Lymphoma
    - Neuroblastoma
    - Soft tissue sarcoma
    - Bone tumors
- Cancer treatment exposures
    - Radiation (maximum target dose, dose categories, or as a continuous variable)
        - Cranial radiation therapy
            - 0-29 Gy
            - 30-49 Gy
            - 50Gy or greater
        - Non-cranial radiation therapy (yes/no)
    - Chemotherapy (yes/no, or as a continuous variable)
        - IV methotrexate
        - Intrathecal methotrexate
        - Cytarabine
        - Vincristine
        - Anthracycline (doxorubicin equivalent dose)
        - Alkylating agent (cyclophosphamide equivalent dose)
        - Corticosteroids
        - Platinum agents
    - Shunt (yes/no)
- Time since diagnosis
- Current Medication Treatment
    - Antidepressant
    - Anxiolytic
    - Analgesic
- Chronic Health Conditions (all CTCAE grades to be used for burden score described below)
    - Cardiovascular
    - Pulmonary
    - Renal
    - Hepatic
    - Gastrointestinal
    - Endocrine
    - Musculoskeletal
    - Neurologic
- Marriage (Which of the possibilities best describes your current marital status?)
    - Married
    - Living with a partner as married
    - Separated or no longer living as married
    - Divorced
    - Widowed
    - Single, never married or never lived with partner as married

- Employment (What is your current employment status?)
    - Not currently working
    - Working full-time (30+ hours per week)
    - Working part-time (less than 30 hours per week)
    - Caring for home or family (not seeking paid work)
    - Unemployed and looking for work
    - Unable to work due to illness or disability
    - Retired
    - Student
- Independent Living Status/ Assistance Needs
    - Concerning your current residence, do you:
        - Own your residence
        - Rent
        - Live with parents
        - Other
    - Because of any impairment or health problems, do you need the help of other persons with personal care needs, such as eating, bathing, dressing, or getting around your home? (yes/no)
    - Because of any impairment or health problems, do you need the help of other persons in handling routine needs, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes? (yes/no)
    - Does any impairment or health problem keep you from holding a job or attending school? (yes/no)
- Geocoded Social Determinants of health
    - Social Vulnerability Index (SVI)
        - Measure of neighborhood-level deprivation that provided data on four categories including socioeconomic status, household characteristics, racial and ethnic minority status, and housing type and transportation[30,31]
- Personal Income
    - None
    - Less than $19,000
    - $20,000 - $39,000
    - $40,000 - $59,000
    - More than $60,000

Statistical Analysis

Aim 1: Identify longitudinal profiles of comorbid psychiatric symptoms and pain across three timepoints

To identify unobserved subgroups of survivors with similar longitudinal patterns of comorbid psychiatric symptoms and pain, we will use latent profile modeling across three assessment timepoints. Because all indicators are continuous, the primary analytic approach will be latent profile analysis (LPA) with repeated measures. Repeated measures of depression, anxiety, and somatization (BSI-18 subscales) and pain and interference (SF-36) will be included simultaneously as continuous indicators. Models will be estimated to use full-information maximum likelihood and analyses will be restricted to participants contributing data at all three time points.

We will estimate models specifying increasing numbers of profiles (e.g., 2–6 profiles). Model selection will be guided by Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample-size adjusted BIC, entropy, likelihood ratio tests (e.g., BLRT/LMR where applicable), minimum profile prevalence (≥5%), and clinical interpretability of profile trajectories. Posterior profile membership probabilities will be examined to assess classification quality. Time-varying antidepressant, anxiolytic, and analgesic use will be included as covariates to account for symptom treatment and management.

For Hypothesis 1.1, we will identify latent profiles that capture distinct longitudinal patterns of comorbid psychiatric symptoms and pain across three timepoints; these profiles will define trajectory profile membership used as the primary outcome or exposure variable in subsequent aims.

Aim 2: Identify demographic, diagnosis, and treatment-related predictors of psychiatric symptoms and pain

To evaluate predictors of psychiatric symptom–pain trajectory membership, we will model latent profile membership as the dependent variable using multinomial logistic regression. The lowest symptom–pain burden profile will serve as the reference category. Primary predictors will include sex, age at diagnosis, age at baseline, cancer diagnosis, treatment exposures (e.g., cranial and non-cranial radiation, chemotherapy indicators or dose-equivalent measures), and baseline socioeconomic indicators, including personal income, education, and the Social Vulnerability Index (SVI).

Models will be adjusted for cohort (original vs expansion), time since diagnosis, and other relevant confounders. To address uncertainty in profile assignment, we will use posterior probability–weighted regression or a three-step approach where feasible. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) will be reported.

For Hypothesis 2.1, we will compare the distribution of female and male survivors across latent trajectory profiles using Chi-square tests and assess the association between sex and trajectory profile membership using the sex coefficient from the multinomial logistic regression models.

For Hypothesis 2.2, baseline socioeconomic factors will be evaluated for association with trajectory profile membership using multinomial logistic regression. In addition, Chi-square tests will be used for categorical socioeconomic variables, and t-tests or ANOVA will be used for continuous socioeconomic variables, as appropriate.

Aim 3: Identify chronic health conditions associated with psychiatric comorbidities and pain

Associations between chronic health conditions and latent profile membership will be evaluated using multinomial logistic regression, with profile membership as the outcome. Chronic health conditions will be summarized using CTCAE-based classifications and modeled in two ways:

1. baseline burden and
2. longitudinal change in burden from baseline to the most recent follow-up, categorized as no change, improvement, or worsening. New variable categories for patients.

The baseline burden will be determined using methods previously described in Geenen et al. 2007: Survivors with at least one grade 1 event are considered to have low burden; survivors with at least one grade 2 event and/or one grade 3 events are considered to have a medium burden; survivors with two or more grade 3 events, or one grade 4 events and one grade 3 events, are considered to have a high burden; and survivors with multiple grade 3 or 4 events are considered to have a severe burden[32,33]. Baseline burden and change variables will be included simultaneously to distinguish persistent disease burden from worsening over time. Models will adjust for demographic, diagnostic, and treatment-related variables to reduce confounding. Adjusted ORs and 95% CIs will be reported.

For Hypothesis 3.1, we will examine the association between baseline chronic health condition burden and latent trajectory profile membership using multinomial logistic regression, evaluating the significance of baseline burden variables in distinguishing profiles characterized by persistently elevated and increasing psychiatric symptoms and pain.

For Hypothesis 3.2, we will include longitudinal change in chronic health condition burden as a predictor in the multinomial logistic regression models and assess whether worsening burden is significantly associated with membership in trajectory profiles characterized by persistently elevated and increasing psychiatric symptoms and pain, independent of baseline burden.

For the Exploratory Aim, we will examine the bidirectional relationship between chronic health condition burden and longitudinal profiles of psychiatric symptoms and pain by evaluating both whether chronic health condition burden predicts latent profile membership and whether latent profile membership is associated with subsequent chronic health condition burden over time. Baseline burden and longitudinal change in burden will be evaluated as predictors of latent profile membership using multinomial logistic regression. In the reverse direction, repeated measures ordinal logistic regression models will be used to assess whether survivors assigned to profiles characterized by persistently elevated or increasing psychiatric symptoms and pain have greater odds of higher chronic health condition burden at follow-up, independent of baseline burden and relevant demographic, diagnosis, treatment-related, and socioeconomic covariates.

Aim 4: Identify functional limitations associated with different profiles of psychiatric comorbidity and pain

We will examine the association between latent trajectory profiles and functional outcomes using multivariable logistic regression. Outcomes will include independent living status, need for assistance with personal or routine care, and impairment preventing employment or education assessed at the most recent timepoint. Latent profile membership will be the primary independent variable.

Models will adjust for age, sex, time since diagnosis, socioeconomic indicators, and treatment exposures. In secondary models, chronic health condition burden will be added to assess whether associations between trajectory profile and function are independent of physical morbidity. Results will be reported as adjusted ORs with 95% CIs.

For Hypothesis 4.1, we will use multivariable logistic regression to model each functional outcome as a binary dependent variable, with latent psychiatric symptom–pain trajectory profile membership as the primary independent variable, and evaluate whether profiles characterized by persistently elevated or increasing symptoms are associated with higher odds of reduced functional status after adjustment for demographic, socioeconomic, and treatment-related covariates.

Impact Statement

At the completion of this project, we will have identified patterns of comorbid psychological symptoms, their predictors, relationship to other health outcomes, and relationship to functional outcomes. Better understanding the relationship between anxiety and depression in childhood cancer survivors will allow us to develop better, more targeted interventions to address long-term distress in survivors. Additionally, by examining and characterizing the impact of comorbid anxiety and depression on functional outcomes and their complex relationship with chronic health outcomes, we will be able to better identify survivors who may benefit from additional support.

Example Table and Figures

Example Table 1. Demographic and Clinical Characteristics

	Baseline		First FU		Second FU	
	Mean (± SD)	**Range**	**Mean (± SD)**	**Range**	**Mean (± SD)**	**Range**
Age (years)						
Age at Diagnosis (years)						
Time since Diagnosis (years)						
	Frequency	**%**	**Frequency**	**%**	**Frequency**	**%**
Sex						
Males						
Females						
Diagnosis						
Leukemia						
Lymphoma						
Non-Hodgkin Lymphoma						
Soft-tissue Sarcoma						
Bone Cancer						
Neuroblastoma						
CNS Tumor						
Wilms Tumor						
Cancer Treatment Exposures						
Cranial radiation, Gy						
None						
<20						
≥20 to <30						
≥ 30						
Non-cranial radiation						
Yes						
No						
IT Methotrexate						
IV Methotrexate, g/m2						
Median (IQR) dose						
None						
>0 to <40						
≥ 40						
Cytarabine						
Yes						
No						
Anthracycline, mg/m2						
Median (IQR) dose						
None						
1-249						
≥250						

Table 2. Psychological Outcome Across Timepoints

	Baseline ($N_{original}$ = 9,146; $N_{expansion}$ =8,274)			**First Selected Follow-Up** ($N_{original}$ = 7,260; $N_{expansion}$ =4,495)			**Second Selected Follow-Up** ($N_{original}$ = 5,257 ; $N_{expansion}$ =5,361)		
	Original Cohort (%)	**Expansion Cohort (%)**	**Total N**	**Original Cohort (%)**	**Expansion Cohort (%)**	**Total N**	**Original Cohort (%)**	**Expansion Cohort (%)**	**Total N**
GSI									
Distressed	740 (8.1)	690 (8.3)	1,430	736 (10.1)	378 (8.4)	1,114	361 (6.9)	544 (10.2)	905
Not Distressed	8389 (91.9)	7575 (91.7)	15,973	6516 (89.9)	4112 (91.6)	10,628	4891 (93.1)	4814 (89.9)	9,705
Depression									
Distressed	938 (10.3)	881 (10.7)	1,817	853 (11.8)	482 (10.7)	1,335	433 (8.2)	649 (12.1)	1,082
Not Distressed	8202 (89.7)	7390 (89.3)	15,592	6404 (88.2)	4012 (89.3)	10,416	4822 (91.8)	4712 (87.9)	9,534
Anxiety									
Distressed	628 (6.9)	544 (6.6)	1,172	557 (7.7)	322 (7.2)	897	298 (5.7)	463 (8.6)	781
Not Distressed	8507 (93.1)	7725 (91.7)	16,232	6701 (92.3)	4168 (92.8)	10,869	4957 (94.3)	4898 (91.4)	9,855
Somatic									
Distressed	755 (8.3)	765 (9.2)	1,520	1018 (14)	362 (8.1)	1,380	502 (9.6)	537 (10)	1,039
Not Distressed	8384 (91.7)	7506 (90.8)	15,890	6236 (86)	4132 (91.9)	10,368	4753 (90.4)	4821 (90)	9,574

Example Table 3. Fit Statistics for Tested Models

	Number of Parameters	**Entropy**	**BIC**	**BLRT (p)**	**LMR (p)**
1-Profile					
2-Profiles					
3-Profiles					
4-Profiles					
5-Profiles					
6-Profiles					

Example Table 4. Multivariable Models of Demographic, Diagnosis, and Treatment Predicting Psychiatric Comorbidity and Pain Over Time

	Profile 1	Profile 2	Profile 3	Profile 4	Profile 5	Profile 6
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Age at Diagnosis (years)						
Sex						
Males						
Females						
Cancer Treatment Exposures						
Cranial radiation, Gy						
None						
<20						
≥20 to <30						
≥ 30						
Non-cranial radiation						
Yes						
No						
Chemotherapy						
Yes						
No						
Household Income						
Education						
College						
High School						
< High School						
Area Deprivation Index						
Social Vulnerability Index						
Employment Status						
Not currently working						
Working full-time						
Working part-time						
Caring for home or family (not seeking paid work)						
Unable to work due to illness or disability						
Retired						
Student						
Marital Status						
Married						
Living with a partner as married						
Separated or no longer living as married						
Divorced						
Widowed						
Single, never married or never lived with partner as married						

Example Table 5. Multivariable Models of Chronic Health Conditions Associated with Psychiatric Comorbidity and Pain Over Time

	Profile 1	Profile 2	Profile 3	Profile 4	Profile 5	Profile 6
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Chronic Health Conditions						
Worsening over time						
Improving over time						
Persistent over time						

Example Table 6. Multivariable Models of Chronic Health Condition Burden Associated with Psychiatric Comorbidity and Pain Over Time

	Profile 1	Profile 2	Profile 3	Profile 4	Profile 5	Profile 6
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Burden Score of Events						
Low						
Medium						
High						
Severe						

Example Table 7. Prediction of Functional Outcomes by Profiles of Psychiatric Comorbidity and Pain

	Live Independently	Require Assistance for Personal Care Needs	Require Assistance for Daily Tasks	Impairment preventing employment or education
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Profile 1				
Profile 2				
Profile 3				
Profile 4				
Profile 5				
Profile 6				

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