ANALYSIS CONCEPT PROTOCOL

1. STUDY TITLE

Symptom progress and adverse health outcomes in adult childhood cancer survivors

2. WORKING GROUP AND INVESTIGATORS

Working Groups: Biostatistics/Epidemiology and Psychology.

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3. BACKGROUND AND RATIONALE

Although advances in treatment and follow-up care have markedly improved the 5-year survival rate of childhood cancers,[1] survivors are vulnerable to late effects, including a variety of symptoms, chronic health conditions, and premature death.[2] Using systematic clinical assessments, the St. Jude Lifetime Cohort Study (SJLIFE) found that by age 45 years, 95% of adult survivors of childhood cancer developed ≥1 chronic condition and 80% had a severe or life-threatening condition.[3] Using self-reported outcomes, the Childhood Cancer Survivor Study (CCSS) found that the cumulative incidence of a severe, life-threatening, or fatal condition was greater among survivors than siblings (53.6% vs 19.8%) by age 50 years.[4] Our recent report from the SJLIFE cohort found a longer time since diagnosis was associated with higher cumulative prevalence in 12 symptom domains. The most frequent symptom was pain in different areas including head (36%), back or neck (49%), and other sites (59%).[5] Symptoms play a unique role in cancer survivorship because they are proximal to cancer diagnosis and treatment exposure, and are predictive of deteriorated health outcomes.[6] Although survivors report multiple, concurrent symptoms (i.e., symptom clusters),[7] it is unclear to what extent symptom clusters are associated with long-term adverse health outcomes including the occurrence of chronic health conditions and mortality.[8,9]

Previous symptom studies are largely based on a cross-sectional design that denotes a snapshot of symptom experience. Although some studies have reported the association between symptom presence and the change in quality of life,[10] no studies have investigated the change in individual symptom domains/clusters over time, and whether the change of individual symptom domains/clusters are associated with adverse health outcomes including chronic conditions and premature mortality. In addition, very few studies have examined if specific cancer therapeutic exposures contribute to the change of individual symptom

domains/clusters over time.[11,12] Identifying prognostic values of individual symptoms/clusters related to chronic health conditions and mortality is critical for planning clinical assessment and interventions to promote healthy aging in cancer survivors.

Our recent NCI-funded R21 grant (MPIs: Huang & Krull) proposes to use the longitudinal and repeated symptom data collected over 25 years from the CCSS participants who also completed comprehensive clinical assessment in SJLIFE to examine the association of symptom progress with adverse health outcomes (i.e., chronic health conditions and premature mortality) in adult survivors of childhood cancers. This R21 grant includes two Specific Aims:

- **Aim 1:** To investigate the presence of individual symptom domains and symptom clusters from multiple time points spanning 25 years among adult survivors of childhood cancers, and to investigate the survivors' change of symptom clusters over time related to cancer treatment;
- **Aim 2a:** To investigate the prognostic value of individual symptom domains and symptom clusters for the development of chronic health conditions (CHCs) organized by individual organ systems (or CHC groups thereafter) in adult survivors of childhood cancers;
- **Aim 2b:** To investigate the prognostic value of individual symptom domains and symptom clusters for all-cause and cause-specific mortality in adult survivors of childhood cancers.

We have completed the data analysis for **Aim 1** and **Aim 2a** based on 735 adult survivors from St. Jude who have available symptom data over 3 time points (T1, T2, T3) and completed comprehensive clinical assessment. Using latent class analysis, symptoms were classified into 4 subgroups at each time point: 1) high physical & psychological symptoms; 2) moderate-high physical & psychological symptoms; 3) moderate-high physical symptoms; or 4) low physical & psychological symptoms. CHCs were graded using the modified CTCAE from SJLIFE and grouped by different organ systems. We tested associations of symptom classes with new onset and worsening of CHC severity that occurred after symptom reports at each time point. We found that survivors having high physical & psychological symptoms at baseline (Class 1) had higher risk for onset/worsening of respiratory (RR 1.32, 95%CI 1.04-1.67), musculoskeletal (RR 1.91, 95%CI 1.35-2.69), and peripheral neuropathy (RR 2.53, 95% CI 1.81-3.53) CHCs compared to survivors with low physical and psychological symptoms (Class 4). Worsened or consistently high symptom burden over time increased risk of new onset or worsened peripheral neuropathy (RR for symptom progression T1-T2 2.23, 95%CI 1.69-2.93; RR for symptom progression T2-T3 2.81, 95%CI 2.04, 3.87) and respiratory (RR for symptom progression T1-T2 1.30, 95%CI 1.06-1.59; RR for symptom progression T2-T3 1.33, 95%CI 1.06, 1.68) CHC's. Associations of symptom progression with CHCs were not attenuated when adjusting for age, sex, treatment and smoking status.

*Given the smaller sample size and mortality of St. Jude participants who completed multiple CCSS and SJLIFE evaluations. We currently are proposing to expand **Aim 2b** to include all survivors enrolled in CCSS (both the original and expanded cohorts). The outline and justification for the expansion of Aim 2b is presented below.*

4. SPECIFIC AIM/RESEARCH HYPOTHESES

Specific Aim: To investigate the prognostic value of symptom domains and clusters for all-cause and cause-specific mortality in adult survivors of childhood cancers.

Note 1: *The association between symptom domains and clusters with CHC groups (Aim 2a) has already been analyzed in survivors who are jointly enrolled in both CCSS and SJLIFE and* ***will not*** *be re-analyzed in the larger CCSS cohort (proposed in this CCSS concept). Since mortality is a less frequent event than CHCs, we are proposing to expand the study population described in the original R21 to examine associations between symptoms domains and clusters with mortality (Aim 2b) using the entire CCSS survivor cohort, not just those also enrolled in SJLIFE. We plan to use the established symptom domains and clusters classification system derived from Aim 1 to accomplish the analysis for Aim 2b.*

Note 2: *This Aim will evaluate the prognostic value of individual symptom domains and clusters in associations with mortality among adult survivors of childhood cancer. It is not our purpose to develop prediction models for mortality based on symptom progression, which requires the use of independent, external cohorts for validation. While SJLIFE provides a great opportunity for external validation of prediction models, only 59 SJLIFE adult survivors of childhood cancer died after completion of the first two symptom surveys (N=2,174).*

This Specific Aim will test two hypotheses:
Hypothesis 1: Persistence in individual symptom domains and severe symptom clusters over time will be associated with higher risk of all-cause and cause -specific mortality.

Hypothesis 2: Persistence of symptom clusters over time will have a greater prognostic value for developing all-cause and cause-specific mortality than the persistence of individual symptom domains.

5. METHODS

5.1. Study Design:

This Aim includes data collected from two time points (T1, T2) among CCSS adult survivors of childhood cancer who participated in the original cohort including the baseline survey (T1) and FU4 survey (T2) and in the expanded cohort including the baseline survey (T1) and FU5 survey (T2).

5.2 Subjects:

Our inclusion criteria for the CCSS sample:

- Survivors participated in the original and expanded cohorts;
- ≥5 years from initial diagnosis of pediatric cancer/malignancy;
- ≥18 years old at the time of survey;
- Participated in the CCSS baseline (T1) and one additional follow-up survey (T2; FU4 for the original cohort participants and FU5 for the expanded cohort participants).

Exclusion criteria are:

- Proxy completion of symptom survey;
- Residing outside the U.S., which limits access of on-site risk-based clinical assessment for chronic conditions. Note: this criterion is included as it was used in the SJLIFE study for Aim 1 and Aim 2a.

5.3 Symptom measures:

Common symptom items used in both CCSS and SJLIFE studies (Aims 1 and 2a) are used for this analysis (Aim 2b). Symptom assessments comprised 37 items recommended by the COG Long-Term Follow-up Guidelines that were used in our

previous publication. Items assessed 10 domains: sensation (8 items), motor/movement (4 items), cardiac symptoms (3 items), pulmonary symptoms (2 items), pain (4 items), fatigue (2 items), nausea (1 item), memory (1 item), anxiety (6 items), and depression (6 items). A specific symptom domain was considered as present (i.e., abnormal) if any symptom from the corresponding domain was denoted as present. Latent class analysis will be used to generate symptom clusters (see the 1st paragraph under 5.6 Analytic Approaches).

5.4 Outcome of Interest:

- Mortality: All survivors eligible for participation in CCSS are included in a search for deaths using the National Death Index (NID) from 1979 to 2019 (or the most recent year). Maintained by the National Center for Health Statistics, NDI provides underlying and multiple causes of death for deceased individuals using the International Classification of Disease, the 9th version. We will focus on all-cause mortality comprised of a direct consequence of the original cancers (e.g., recurrence, progression of primary cancers), cancer treatment-related causes (e.g., subsequent malignant neoplasm, cardiac, pulmonary toxicity), and non-treatment-related causes (e.g., accidents, suicide).

5.5 Background and confounding Variables:

- Medical record abstractions have already been conducted to obtain information of chemotherapy including cumulative doses for specific agents, radiotherapy including fields and doses, surgical procedures, hematopoietic cell transplantation, and acute life-threatening organ toxicity. Treatment will be categorized on a continuum of increasing intensity, from surgery only (low intensity), chemotherapy only with/without surgery (moderate intensity), to radiotherapy with/without chemotherapy or surgery (high intensity).[13] Associations of symptom presence with chemotherapy agents/doses and radiation fields/doses will also be explored.

- Socio-demographic and lifestyle factors: age, sex, length of follow-up, race/ethnicity, educational attainment, physical activity, and substance use (tobacco, alcohol, smoking) from the CCSS surveys will be used as covariates in the analyses.

- CHCs: Consistent with the previous CCSS studies, 137 individual conditions were graded using the modified Common Terminology Criteria for Adverse Events version 4.03, and identified as present if the grade was 2 (moderate), 3 (severe/disabling), or 4 (life-threatening or disabling).[14] Organ-specific CHC groups were classified as present if any corresponding conditions within an organ group was present. The 11 CHC organ groups included vision, hearing, speech, pulmonary, cardiovascular, gastrointestinal, renal, musculoskeletal, neurological, hematologic, and endocrinological. *For Aim 2b, we plan to report CHCs information as a background variable rather than included CHCs in the analytic modeling, because 1) the associations of symptom progression and CHC groups have been addressed in Aim 2a, and 2) symptom progressions and CHC groups are highly associated, and CHC groups are on the pathway from symptom progress to mortality onset.*

5.6 Analytic Approaches**:**

We plan to use the established classification system for symptom domains and clusters derived from ***Aims 1 and Aim 2a*** *(CHC outcomes) to accomplish analyses for* ***Aim 2b*** *(mortality outcome).* Briefly, each symptom domain will be categorized as absence (i.e., normal) vs. presence (i.e., abnormal), and logistic regression in SAS PROC LOGISTIC will be used to model the probability of presence status as a function of treatment intensity and other covariates. For symptom clusters, latent class analysis (LCA) in MPlus will be used to obtain the latent class for each survivor. The class number will be decided using Bayesian information criterion, Lo-Mendell-Rubin test, bootstrap likelihood ratio test,[15] and a minimum of ≥5% of the observations in each class. Once the classes are decided, the classes can be ordered in a progressive manner (from least to most severe).

For the symptom clusters created in Aim 1, we first test if the number and structure of clusters are consistent and non-invariant over time. If this is the case, we model the proportion of survivors in progressively more severe class vs. those in least severe class as a function of time (current age and length of follow-up), treatment intensity, and other covariates using GEE approach[16] for repeated nominal categorical responses and implemented in SAS PROC GENMOD. However, if the number and structure of clusters are inconsistent or invariant, we obtain the latent classes at baseline, and apply the criteria from baseline to the two latter time points to classify survivors into the classes identified at baseline, and use the approach above to evaluate if the proportion of survivors in the most severe class increases with time in a more pronounced manner in those receiving intensive treatment. Once it is established that the class structure is similar, the transition patterns across the three time points would be estimated using the LCA with likelihood method or Bayesian approach.[17]

For Hypothesis 1, we assume persistent presence of individual symptom domain and cluster over time will have prognostic value in onset of mortality. The relationship with mortality after the second CCSS symptom survey (i.e. define survival time as time from the second symptom survey to the time of conducting analyses) as a function of persistent presence of individual symptom domains plus covariates (individual models), as well as symptom cluster persistence plus covariates will be tested using Cox's proportional hazards model and implemented in SAS PROC PHREG.

For Hypothesis 2, we assume the model for the persistence of symptom clusters over time would be superior to eight models for the persistence of individual symptom domains in predicting mortality. The method of Kang (2015)[18] will be used to test if the symptom cluster model is superior to individual symptom models in predicting survival.

6. REFERENCES

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