Association between previous cancer treatment and depression in Adolescent and Young Adult survivors of pediatric cancers and their parental caregivers: a cross-sectional study

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Abstract

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Background

Mortality from childhood cancers continues to decline, despite there being an increased focus on the long-term effects of cancer treatment on survivors. Mental health outcomes, like depression, are of particular importance to clinicians for Adolescent Young Adult (AYA) survivors of pediatric cancers. Furthermore, parental caregivers of survivors are also impacted by the burden of treatment. This study seeks to determine what aspects of previous cancer treatment are associated with depression in both AYA survivors and their caregivers.

Methods

AYA survivors of pediatric cancer (155) and their caregivers (150) completed a survey on readiness to transition to adult survivorship clinics. This ancillary analysis assessed the presence of depression in both cohorts using the PROMIS Depression instrument. Predictors of depression included self-reported measures from survivors and parents and clinical data abstracted from medical records of survivors. Logistic regression was performed for each cohort, with three separate models performed to highlight differing aspects of the cancer treatment and experience. These included the Intensity of Treatment (ITR), treatment modalities, and risk of late effect combined with perceived physical health. Models were adjusted for demographic covariates previously identified as potential risk factors for depression.

Results

AYA survivors had higher prevalence of depression as compared to their caregivers (26.3% vs 18.7%, respectively). Survivors were 52.5% female, while caregivers were 94.2% female. Overall, ITR, treatment modalities, and late effect risks were not statistically significant predictors of depression in either cohort, except for lower odds of depression for survivors at risk for cardiac problems. Still, aspects of treatment like having a relapse and having surgery were positively associated with depression in both survivors and their caregivers in full logistic models. Not having private insurance was significantly associated with increased odds of depression in survivors in all models. Worse perceived health was negatively associated with depression in survivors and parents.

Conclusion

Future mental health care for cancer survivors should focus on individuals with inadequate health care coverage as a group with a particularly elevated risk for depression. Parents should also be included in the screening process for depression as their child transitions to adult survivorship.

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Chapter 1: Introduction

Background

As treatments continue to improve both the mortality rate and longevity of survivorship for pediatric cancer patients, there is an increased need to better prepare these patients for the potential effects their treatment may have on them. A cancer diagnosis at a young age can impact children and adolescents as they mature and grow both physically and mentally. With more survivors living longer into survivorship, there is a need to identify those survivors who may be at greater risk for mental health outcomes like depression. Furthermore, the cancer experience is not one that only the patient experiences; rather, a child's parental caregiver is also deeply impacted by the cancer trajectory, as they witness and must bear the burden of economic and psychological impacts of their child's diagnosis. These caregivers are also at risk for adverse mental health outcomes as a result of this cancer diagnosis, and therefore require additional support and resources to cope.

Problem Statement

Depression levels in survivors and their caregivers depend on a number of factors. A number of risk factors for depression have been identified for depression in survivors, with similar demographic and social risk factors for depression prevalent to the caregivers of these patients. Since the cancer trajectory of AYA survivors is also experienced by the caregivers, they also need to be surveilled for depression. Ultimately, the need for surveilling to better identify those most at risk for depression is of great need.

Purpose Statement

The purpose of this analysis is to assess the association between **previous cancer treatment** and depression in pediatric cancer survivors and their caregivers. By assessing prior cancer treatment in multiple ways, we can better articulate what associations (if any) give researchers the best way of identifying at risk survivors and their caregivers for depression. By including parents in this analysis, we can compare findings across both cohorts to see what the similarities and differences in depression are, and also what is associated with that depression.

Significance

The findings from this analysis can offer clinicians and researchers a greater understanding of the range of potential risk factors that exist for both survivors and their caregivers. Unique to this analysis will be its multiple models and analysis for both survivors and caregivers. By including both cohorts, this analysis can provide evidence for survivors and caregivers most at risk for depression. In identifying those most at risk, clinicians can better adapt their surveillance methods to identify and target these populations for mental health services.

Chapter 2: Literature Review

2.1 Introduction

Cancer continues to be a leading cause of chronic disease in children, with an estimated 9,910 children and 5,280 adolescents diagnosed in 2023 alone.[1] Although there has been a steady decrease in the child mortality from cancer,[1] there are still lasting impacts from the treatment of cancer on children as well as their primary caregivers. In particular, depression is major focus for long-term impacts of cancer treatment and has been studied extensively. Depression remains a relevant topic to investigate as it pertains to survivors and their caregivers for a number of reasons. This study will assess those reasons and expand on the need for investigating how depression is impacted by intensity of treatment and other late effects of cancer in childhood survivors and their caregivers.

2.2. Burden and Outcomes of Childhood Cancer in the United States

2.2.1 Incidence

Collectively, the National Cancer Institute’s (NCI) Surveillance, Epidemiology, and End Results (SEER) data and CDC’s National Program for Cancer Registries (NPCR) report population-based cancer incidence data for approximately 100% of the US population. These registries acquire data, including patient demographics, primary tumor site, tumor morphology, stage at diagnosis, and first course of treatment. For children aged 0-14 years, SEER approximates 9,910 will be diagnosed and 5,280 adolescents aged 15-19 will be diagnosed in 2023, 1,040 and 550 will die from cancer, respectively. Of children diagnosed with cancer, leukemia accounts for 28% of these cases and is the most common childhood cancer, while brain and other nervous system tumors accounts for 26% of these cases. Although overall childhood cancer incidence rate had been increasing since 1975, it appears to have stabilized from 2010 to 2019. Despite this, incidence continues to increase by 1% yearly among adolescents.[1]

2.2.2 Decreased mortality

According to CDC population-level data, mortality in children has decreased from 1970 to 2020 from 6.3 to 1.9 per 100,000 children, and from 7.2 to 2.6 per 100,000 adolescents. This translates to overall reductions of 70% and 64%, respectively over this 50-year time span from 1970 to 2020. These dramatic declines in mortality can be attributed to an 84% reduction in mortality from leukemia for children and 75% in adolescents. Furthermore, remission rates of 90-100% have been achieved for childhood acute lymphocytic leukemia over the past four decades. Despite the findings of this analysis, these estimations of incidence data are model-based, and encompass a projection of three to four years ahead. So, these analyses can only account for trends in recent data. Important to consider, these trends do not account for COVID-19 and the impact that that the pandemic had on reduced access to care, including diagnoses for children.[1]

Aside from population-level data, late mortality was also assessed by the Childhood Cancer Survivor Study (CCSS), a retrospective cohort study that ascertained data from 38,036 childhood cancer survivors from 1970 to 1999, along with more than 5,000 siblings of survivors used as a comparison groups. In these analyses, 5-year mortality in childhood survivors at two distinct time points (deaths occurring through 2002,[2] and deaths occurring through 2007[3]) were measured. Overall, trends in both studies were positive, with deaths attributable to health-related causes decreasing from 58% to 41% across both studies. Both studies drew upon a longitudinal sample with long-term follow-up. Still, these findings should be considered in light of the inability to causally link the outcomes of health-related causes of death to the childhood cancer itself. Overall, these studies highlight a progression in the decrease in late mortality from childhood cancers.[2,3]

Mortality of childhood cancer survivors were also assessed globally to portray geographic trends in childhood cancer mortality. Globally, the overall trend over the past 30 years suggests a decrease in mortality for childhood cancers.[4-7] These analyses were highlighted by estimates of annual decreases of 2% to 3% per year in Australasian countries (i.e. Japan, Korea, and Australia), 1.5% to 2% in North America and Chile, and 1% in Argentina,[4] while Europe saw a 2.8% per year decrease.[5] Trends did not appear as favorable for other regions of Latin America, and data on the African continent and a majority of Asia were missing from these studies. Another study assessing 5-year survival across 61 nations for leukemias collapsed all survival trends from CAYA. Survival ranged from 46% (95% CI 43–48) in Mexico >85% in eight countries: Canada, Cyprus, five European countries (Belgium, Denmark, Finland, Iceland, and Switzerland), and Australia. Interestingly, a majority of countries in Europe, Asia, and parts of central and south America reported 5-year survival of 70% or higher. On the other hand, survival was lower than 65% in Chile and Peru, China, India, and Russia. For the US, survival increased from 70.7% in 2000-2004, to 83.3% in 2010-2014. Data from the African continent was limited, with only two countries included (Algeria and South Africa). A majority of data here was for unspecified leukemias.[7] Based on global trends in childhood cancer mortality, the US appears to be aligned with other similar high income countries in its overall decline in 5-year survival for childhood survivors, while other lower income countries appear to have lower survival rates.

2.2.3 Late effects

Despite the reduction in overall mortality among pediatric cancer patients, the long-term health consequences can be substantial. Long-term effects of pediatric diagnoses vary but can include a range of symptoms such as growth and development, organ functioning, reproductive capacity, and risk of subsequent carcinogenesis and chronic conditions.[8-13] Psychosocial impacts of treatment can also impact mental health in survivors such as anxiety, fatigue, and other cognitive deficits.[14-18] Impacts on a survivor's risk of late effects from pediatric cancer include the type of cancer and its treatment, location of the cancer, age during treatment, overall health prior to diagnosis, and genetic makeup.[19-25] These risk factors can vary, and include a myriad of factors impacting livelihoods and quality of lives for survivors of pediatric cancers.

2.2.4 Increase in focus on survivorship

Although there is a growing concern over late effects in pediatric survivors, surveillance of late effects in pediatric cancers has improved in recent years. In particular, there is a greater focus on the surveillance of late therapy-related complications both domestically and internationally. This surveillance is bolstered by the multidisciplinary team at the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG), aimed at establishing and incorporating strategies for surveilling survivors of childhood, adolescent, and young adult (CAYA) cancer for chronic conditions and subsequent malignancies.[26] This international collaboration has developed a number of guidelines focused on optimizing survivorship and mitigating late effects in CAYA survivors, and in specific survivor subgroups.[26-44]

2.3. Impact of Childhood Cancer

2.3.1 Psychological impacts on families

Although childhood cancer leaves a myriad of challenges for the patient, the impact it has on the family is also glaring. A systematic review of family adjustment to childhood cancers focused on family functioning, marital quality, and parenting in the context of pediatric cancers.[45] Interestingly, many of the quantitative studies included did not find mean differences in family functioning for those families with a cancer diagnosis compared to norms or comparison groups.[46-49] On the other hand, qualitative studies found that families accommodate the needs of newly diagnosed children by altering their roles, responsibilities, and day-to-day functioning.[50-55] Other studies found that throughout the treatment trajectory, families continuously adapt to the changing demands.[56-59] Ultimately, the authors of this review concluded that there is a need to focus on the influence these family-level variables may have on individual family members as the patient (and family) navigate the cancer trajectory.[45]

2.3.2 Socio-economic impacts on families

Other challenges also include the financial implications of having a child that is on active cancer treatment and the costs that are incurred as a result. One systematic review evaluated this impact on parents' socio-economic situation.[60] Overall, the review found that there was a high prevalence of disruptions in employment for parents. A majority of studies found that mothers were more likely to quit work or be unemployed following the child's diagnosis.[61-70] Furthermore, a majority of studies found substantial income loss after the child's diagnosis.[63,64,68-71] Ultimately, the range of consequences of a child's cancer diagnosis vary for parents. Still, the authors of this review emphasize the need to implement greater financial assessments to yield greater data for support services offered to these families.[60]

2.4. Depression in the US general population

2.4.1 Defining Depression

Depression in the general US population is one of the most common mental health disorders that includes a range of often debilitating symptoms and impairments. According to the American Psychiatric Association (APA), depressive disorders are characterized by “the presence of sad, empty, or irritable mood, accompanied by related changes that significantly affect the individual’s capacity to function.”[72] Of the many categories of depressive disorders, major depressive disorder (MDD) is one of the most common conditions. It is characterized by discrete episodes of at least two weeks, but often last longer. These episodes are marked by clear-cut changes in affect, cognition, and neurovegetative functions. On the other hand, persistent depressive disorder, a more chronic depressive disorder, can be diagnosed following a span of two years of symptoms in adults, and one year in children.[72] Altogether, depression diagnoses are a growing concern as they continue to rise both in the US and globally, with an estimated 18.4% increase from 2005 to 2015 globally.[73]

Nationally representative data on MDD and major depressive episodes (MDE) assess prevalence trends in depression among adolescents and adults in the US. Utilizing complex survey designs, the National Survey on Drug Use and Health (NSDUH) and National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC-III) collect data of the US population (adults and adolescents for NSDUH, and only adults for NESARC-III).[74-76] The NSDUH provides prevalence estimates on MDE, while the NESARC-III provides prevalence estimates on MDD. MDE is measured via questions based on DSM-5 diagnostic criteria. Here, an MDE is classified over the past 12 months if a patient had at least one period of at least two weeks where they felt depressed, lost interest or pleasure in daily activities for most of the day nearly every day, OR if they had problems with sleeping, sleeping, eating, energy, concentration, selfworth, or having recurrent thoughts of death or recurrent suicidal ideation.[74] MDD was also measured using the DSM-5 diagnostic criteria, as previously defined.[72]

2.4.2 Depression in Adolescents and Young Adults (AYA)

Among adolescents aged 12 to 17, two studies investigated MDE 12-month prevalence within this age group.[74,76] Both studies analyzed the NSDUH survey, with the most recent SAMHSA report using 2020 data, while Mojtabai measured MDE from 2003 to 2014. Overall, there appeared to be a positive trend in 12-month MDE prevalence in adolescents across both studies. From 2005 to 2014, and from the 2020 SAMHSA report, adolescents 12-month MDE increased from 8.7%, to 11.3%,[76] to 17%,[74] respectively. Similarly, female adolescents saw an increase in 12-month MDE across all three-time frames (2005, 2014, 2020) in both studies, from 13.1%, to 17.3%,[76] to 25.2%,[74] respectively. As compared to adolescent males in the same three-time frames, 12-month MDE was 4.5%, 5.7%,[76] and 9.2%,[74] respectively.

As for young adults aged 18-25, MDE and MDD were also assessed. From 2005 to 2014, MDE also increased among young adults aged 18-25 from 8.8% to 9.6%,[76] while SAMHSA found the highest prevalence of 12-month MDE to be among 18- to 25-year-olds at 17%.[74] Furthermore, the 12-month MDD prevalence measured by the NESCAC-III was 3x higher among young adults aged 18 to 29 years old as compared to older adults (95% CI: 2.48-3.55).[75] Overall, these findings help to portray a representative sample of the temporal trends in 12-month MDE and MDD among adolescents and young adults. Collectively, these studies highlight a steady increase in 12-month MDE and MDD among adolescents, with continual increases across all three-time frames. Furthermore, it affirms that adolescent females have higher rates of MDE as compared adolescent males within the general US population.[74-76]

2.4.1 Depression in adults

Utilizing both NSDUH and NESCAC-III, two studies found similar findings on the prevalence of MDE and MDD among adults, despite measuring different forms of depression.[74,75] The prevalence of 12-month prevalence of MDE among adults was 8.45%, or 21 million,[74] while the 12-month prevalence of MDD was 10.4%, and 20.6% over the lifetime of individuals.[75] Men had a lower proportion of MDD compared to females (6.2% vs 10.5%),[74] and also had lower odds of 12-month MDD (OR = 0.5, 95% CI: 0.46-0.55).[75] Again, the generalizability of these data offer a snapshot into how depression impacts US adults. Still, causal relationships should not be inferred based on the data collection methods for these complex survey designs.

2.5. Depression among pediatric cancer survivors and their caregivers

2.5.1 Depression among childhood cancer survivors

For patients on treatment and transitioning to survivorship, prevalence of depression can be measured in a longitudinal assessment at timepoints both during treatment and post-treatment. In this methodology, interpretations of depression levels can consider how depression levels are impacted by both treatment and in early survivorship. One study assessed 160 standard risk acute lymphoblastic leukemia (ALL) patients aged 2 to 9 for emotional and behavioral functioning.[77] Parents of the enrolled children completed the Behavioral Assessment System for Children (BASC-2) to assess depression at 4 distinct time periods: 1, 6, and 12 months after diagnosis, and 3 months after completing chemotherapy (referred to as T1, T2, T3, and T4, respectively). Overall, the cancer treatment depression scores remained fairly consistent (21.7% at T1, 28.6% at T2, 21.1% at T3, 28.7% at T4). There was no statistically significant difference for the frequency of more severe depression scores when compared to expected levels. This is true for all time points.[77]

In terms of predictors of at-risk depression levels at various time points, at T2 those at-risk had 7.88x the odds (95% CI: 2.61-23.81, p=0.0002) of having at-risk depression at T4 compared to those with average depression scores at T2; at T3, at-risk patients had 3.7xthe odds of elevated scores at T4 compared to those with average scores at T3 (95% CI: 1.33-10.5, p=0.014); at start of consolidation, patients in the clinically significant range had 17x the odds of a clinically significant score at T4 compared with average scores at start of consolidation (95% CI: 2.06-145.65, p=0.025). Predictors of at-risk and clinically elevated depression from multivariate analyses included less reliance on maintaining social support/coping behaviors, primary language spoken at home, and unhealthy family functioning. In this analysis, the researchers longitudinal approach considered how treatment and the transition off of treatment may impact depression scores. Still, parent proxies were required to assume the emotional functioning of the young survivor population, which may bias results. Overall, this study effectively illustrates the overall trends in depression levels in patient population both on treatment and off.[77]

Another strong assessment of pediatric cancer survivors, the Childhood Cancer Survivor Study (CCSS), is a multi-institutional retrospective cohort study with longitudinal follow-up of survivors of childhood cancer, that assessed survivors for a plethora of outcomes over the course of their survivorship. The original cohort included 14,357 survivors from 1970 to 1986, with additional cohort recruited up through 1999. These survivors were diagnosed with cancer before age 21 and were at least 5-years survival post diagnosis. In total, 38,036 survivors have been included.[78-80] A number of studies analyzed depression data from the CCSS.[78,81-94] The Brief Symptom Inventory-18 (BSI) was utilized in a majority of these analyses to assess depression levels in the analytic samples. The BSI, a 53-item self-reported measure, assesses a number of psychopathology and psychological distress, which includes a subscale focused on depression.[95] Overall, these studies found survivors of pediatric cancers to have higher prevalence of depression to that of their sibling controls—depression (in any form) in survivors ranged among the cohorts from 7% to 34.2%, while sibling depression prevalence ranged from 6.2% to 17.7% across all studies.[78,81,83-85,87,88,90-94]

As it pertains to predictors of depression in these studies, some important associations with depression included younger age to begin drinking associated with future depression risk (RR = 1.3, 95% CI: 1.1-1.5)[81] and loneliness at baseline and follow-up being associated with risk of depression (RR = 17.86, 95% CI: 14.09-22.65).[94] Chronic health conditions were associated with higher prevalence of depression, including cardiac problems (12.4% for those with the problem, 10.2% without, p=0.025), endocrine problems (13.1% for those with the problem, 9.8% without, p<0.001), and pulmonary problems (14% for those with the problem, 10% without, p<0.001).[84] Regarding exercise, vigorous exercise was associated with lower prevalence of depression—for those with 9-12 Metabolic equivalent hours per week (MET), the10djustted prevalence ratio = 0.76 (95% CI: 0.62-0.94), for 9-12 MET, PR = 0.74 (95% CI: 0.58-0.95).[90]

Regarding depression in race and ethnic disparities in depression outcomes, survivor-sibling differences in mean score for depression were greater in Hispanics versus non-Hispanic Whites (NHW) (3.59 vs 1.09, p=0.004). Furthermore, non-Hispanic Blacks (NHB) and Hispanics had greater survivor-sibling differences in Health-Related Quality of Life (HRQOL) than NHWs for mental health (NHB: −5.78 vs −0.69, p=0.001; Hispanic: −3.87 vs. −0.69, p=0.03).[88]

A few CCSS studies utilized the Behavioral Problem Index (BPI) to assess depression.[82,86,96] This instrument utilizes standardized questionnaire developed by the National Health Survey to assess child's behavioral and emotional functioning, combining depression and anxiety in its scale construction.[97] Across these three studies, depression in survivors remained around 17%, while survivors had depression remaining around 9-10%.[82,86,96] Depression was more often used in model building, and was not associated with adult obesity, physical activity or smoking.[82] Among patients that had Cranial Radiation Therapy (CRT), those with CRT had increased symptoms of depression/anxiety, attention deficit, social withdrawal, and peer-conflict (30.9%) compared to those without CRT (8.8%).[86]

Overall, CCSS studies assessed a myriad of factors associated with depression, including a variety of predictors of depression prevalence in AYA survivors of pediatric cancers. Still, the use of sibling controls in a variety of studies is unique in that these subjects are closely impacted by the treatment of their cancer surviving siblings. Therefore, they are not truly representative of the general population, but rather reflect the convenience of recruiting within the family of the participating survivors in the CCSS study. Furthermore, the cohort of CCSS patients was from 1970 to 1999, so treatment of these patients is over 20 years old. Regarding some of the predictors of depression relating to treatment, treatment protocols may be outdated compared to present treatment procedures and approaches to mitigating depression in survivors of pediatric cancers.[78,81-94]

Aside from the CCSS, two systematic reviews assessed mental health outcomes in survivors of childhood cancer; one focused solely on long-term psychological outcomes in pediatric brain tumor survivors,[19] while the other included all cancer types and focused on prevalence and spectrum of mental health problems in survivors.[15] Shah's assessment focusing on brain tumor survivors is important to highlight as very few studies included survivors with brain tumors, of which the entire review focuses on.[19] Of the 11 papers that reported on depression in Shah's review, incidence of depression among brain tumor survivors was greater than 19% in 8 of the 11 papers.[17,98-104] As compared to other cancer types, pediatric brain cancer survivors had significantly higher depression scores and were 2.6 times more likely to develop depression compared to their siblings.[105] Friend's systematic review also found difficulties in survivors with depression and other mood disorders,[16,96,104,106-115] while other analyses did not find anxiety/depression to be more prevalent in survivor cohorts than general populations.[82,110,116]

Outside of the United States, a number of studies assessed depression in survivors of in a global context.[112,117-121] These studies assessed depression with three different instruments; the BSI, a Distress Thermometer that assesses emotional distress,[117] and the Hospital Anxiety and Depression Scale (HADS), to detect depression in vulnerable patient populations.[112,119] These studies did not only have childhood survivors, but also adolescent survivors. They included current child, adolescent, and adult cohorts as well. Overall, depression in child/adolescent survivors ranged from 5% to 18% among cohorts of survivors, while adult survivors ranged from 10% to 27%.[112,117-121]

In terms of risk factors for depression, radiotherapy and risk status were not associated with the Distress Thermometer or depression.[117] For both adolescents and adults survivors, depression was associated with overall functioning status; in particular mental functioning (OR for adults: 6.65, 95% CI: 2.58-17.14, OR for adolescents: 19.71, 95% CI: 3.98-97.54).[118] Studies also found that depression prevalence was higher in female survivors as compared to males.[112,120,121] Overall, these studies included different demographic survivor populations, which offered insight into how depression impacts survivors of different ages. Furthermore, some studies had controls (both sibling-controls, similar to the US, and matched controls), allowing for further comparison across different cohorts.[112,120,121] Still, some studies focused solely on survivors of ALL, which limits the ability to apply these findings to survivors of other cancers.[117,118] Ultimately, findings from these European studies allow for juxtaposition to US cohorts, highlighting similar prevalence of depression in survivors of pediatric cancers.

Lastly, a set of recommendations for surveilling metal health outcomes among CAYA cancer survivors was established by a multidisciplinary team from the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG).[29] Overall, the prevalence of depression among survivors ranged from 2-40% across the studies included in the systematic review.[82,96,117,118,120-122] The authors found that survivors overall were more likely to experience clinically significant depression as compared to sibling cohorts and general population cohorts.[81,82,96,121-123] On the other hand, the evidence was weaker for increased symptoms of depression in survivors as compared to the same two comparison groups.[104,120,124]

The IGHG had a number of recommendations, including that all survivors of CAYA cancer should be surveilled for mental health outcomes, including depression. They highlighted a number of risk factors for survivors for depression. Although the strength of risk factors varies, they vary depending on clinical, demographic, or treatment-related risk factors. For clinical risk factors, they included: late effects/poor perceived health status, pain, early drinking behaviors, and decreased physical activity. For demographic risk factors, they included: female sex, lower educational achievement, unemployment, marital status, and lower annual income. For treatment related risk factors, they included: surgery and chemotherapy.[29]

2.5.2 Depression among caregivers

A number of studies assessed mental health outcomes in caregivers of pediatric cancer patients and survivors.[125-133] Measurements across studies varied with the use of different scales to assess different mental health outcomes. These tools included HADS,[130] BSI,[128,129] the Center for Epidemiological Studies Depression Scale (CES-D),[125] PROMIS Global Health for HRQOL,[127] Patient Health Questionnaire (PHQ-9),[133] the pediatric Distress Thermometer (DT),[126] and the Beck Depression Inventory (BDI-II).[132] Important to highlight is that not all studies included depression in their analyses; rather, other psychosocial outcomes such as high distress,[126] caregiver burden,[129] and HRQOL/anxiety.[127]

Regarding depression in caregivers, prevalence ranged from 7.4% to 59.7% having some level of depression (including borderline depression).[125,128,130-133] This included greater risk for depression in mothers, including 78.1% of caregivers with depression in one study were mothers;[132] another found that mothers had higher prevalence of depression with a mean score of 8.2 using the PHQ-9 scale, while fathers had a mean of 6.2.[133] Other risk factors for caregivers included late effects in survivors being associated with needing greater caregiver support (OR= 26.6, 95% CI: 2.9-241.0).[131] Furthermore, Hispanic parents were at greater risk for depression and had significantly higher depression (48% vs 25%, p=0.002) as compared to non-Hispanic parents. Other risk factors included lower income, higher perceived stress, and lower rating on the children's psychosocial functioning scores.[125] Physical inactivity was also identified as a risk factor for depression (OR= 3.57, 95% CI: 1.95-6.57, p<0.001).[130]

Regarding other psychosocial outcomes, caregiver functioning was assessed in other ways aside from just measuring depression. Overall, findings were mixed across studies with parents of childhood cancer survivors and control groups. In one study, caregiver mental HRQOL and anxiety were comparable to community scores that are in normal limits. There was an association between greater overall psychosocial risk and those with poorer mental HRQOL and increased anxiety.[127] Yet, another study assessing caregiver burden in parents of brain tumor survivors found higher caregiver burden in those parents as compared to matched controls.[129] Another study assessing distress in caregivers found that 16.9% had high distress, with parents of newly diagnosed children being significantly higher (OR = 3.16, 95% CI: 2.12-4.71) and those currently on treatment (OR = 2.81, 95% CI: 2.11-3.76) as compared to parents of children off treatment.[126]

Overall, studies investigating depression and other mental health outcomes in caregivers found varying prevalence of outcomes. In particular, depression widely varied, and some findings were not significantly different between caregivers and community members. A limitation to highlight is that for many studies, depression was not included in the analysis, or was only a minor component of overall psychosocial outcomes. For many studies, psychosocial outcomes included a range of measures assessing depression, PTSS, anxiety, burden, and distress. For this reason, some findings were limited to what prevalence were available in these analyses.

2.6 Existing research on survivor-caregiver dyads

Dyadic studies with caregivers and patients assessed a number of psychosocial outcomes. Some included survivors of childhood cancer,[134-137] while others included active treatment patients for both childhood,[138,139] and AYA patients.[140] Overall, a few studies did not find differences in depression prevalence between parents and patients,[137,138,140] regardless of whether patients were actively on or off treatment. Still, one study with active AYA patients had much higher rates of depression (31% for patients, 28% for parents)[140] as compared to a study of AYA survivors (13%) and their caregivers (8%).[134] In terms of predictors of depression, one study found that low cohesiveness, low expressiveness, and high conflict in current patients were associated with higher levels of depression.[136] Another study found that more frequent fatigue was predicted by increased child depression.[138] Lastly, one study found that financial difficulty and brain cancer diagnoses in their children were predictors of depression and anxiety in caregivers, while there were no significant predictors of depression in patients.[139]

Overall, psychosocial findings other than depression in these dyadic studies varied. One study found similar prevalence of perceived stress between parents and survivors, despite Hispanic parents being at greater risk for depression compared to non-Hispanic parents.[135] One study measuring family cohesion found that depression symptoms were negatively associated with family cohesion, and that AYA perception of family dynamics were more negative than those of the caregivers.[134] Another study identified risk factors for elevated distress in active AYA patients as being female and having less support; 48% of AYA had PTSS, while 42% of parents did.[140]

While these dyadic studies measured a range of mental health outcomes, it is difficult to compare across studies due to the types of patients included (active patients versus survivors). Furthermore, some studies included AYA patients versus child patients, which further limits the ability to make inferences across dyadic studies. Also, these studies utilized a range of tools to assess these outcomes, and also used depression/anxiety in combination with other mental health outcomes (PTSS, perceived stress). One important aspect of these findings to highlight is the similarities in prevalence of mental health outcomes between both dyads in a number of studies,[135,137,138,140] regardless of whether it was for depression or other psychosocial outcomes.

2.7 Summary of current problem and study relevance

Survivors of pediatric cancer experience a myriad of challenges as they transition off of treatment and begin long-term follow-up care for late effects surveillance. Of particular importance to this analysis is the varying levels of depression they may face, with findings on depression levels varying on a number of factors.[15,19,29,77,78,81,83-85,87-94,112,117-121,123] Importantly, a number of risk factors have been identified for depression in survivors,[29] with similar demographic and social risk factors for depression prevalent to the caregivers of these patients.[125-133] Ultimately, the need for surveilling to better identify those survivors most at risk for depression is of great need, as recommended by the IGHG.[29] Some researchers argue that including the caregiver in addressing mental health outcomes may prove necessary, too.[127,141]

In this study, an analysis with a majority of dyads will investigate depression in both AYA survivors of pediatric cancer and their caregivers will be conducted. Unique to this analysis will be the application of multiple sets of risk factors to both cohorts. Here, models will include three sets of potential risk factors for depression; the first will include the Intensity of Treatment scoring, the second will include treatment modalities, and the third will include late effect risk factors and perceived health status as identified in the literature.[29] Many of the studies previously identified in this review found associations between certain risk factors and depression. Yet, they did not assess these three groups of risk factors on both survivors *and* their parental caregivers. By assessing these cohorts for depression using the same risk factors, we can learn whether or not these risk factors are applicable to both survivors and their caregivers as they transition away from treatment and into survivorship. Furthermore, many studies investigated depression only as a smaller component of other psychosocial metrics for mental health outcomes. Here, we will focus on depression as the outcome. In doing so, models will highlight what risk factors may be associated with depression in both cohorts and emphasize the complex nuances in which factors are associated with depression in survivors and their caregivers.

This study seeks to understand how treatment-related factors are associated with depression in caregivers and pediatric cancer survivors. By considering these risk factors, this analysis will aim to identify both the survivors and their caregivers that may require greater attention for depression outcomes as they transition into survivorship. This study will ascertain a number of risk factors to highlight what similarities and differences in depression may present in AYA survivors and their parental caregivers.

Chapter 3: Manuscript

Abstract

Background

Mortality from childhood cancers continues to decline, despite there being an increased focus on the long-term effects of cancer treatment on survivors. Mental health outcomes, like depression, are of particular importance to clinicians for Adolescent Young Adult (AYA) survivors of pediatric cancers. Furthermore, parental caregivers of survivors are also impacted by the burden of treatment. This study seeks to determine what aspects of previous cancer treatment are associated with depression in both AYA survivors and their caregivers.

Methods

AYA survivors of pediatric cancer (155) and their caregivers (150) completed a survey on readiness to transition to adult survivorship clinics. This ancillary analysis assessed the presence of depression in both cohorts using the PROMIS Depression instrument. Predictors of depression included self-reported measures from survivors and parents and clinical data abstracted from medical records of survivors. Logistic regression was performed for each cohort, with three separate models performed to highlight differing aspects of the cancer treatment and experience. These included the Intensity of Treatment (ITR), treatment modalities, and risk of late effect combined with perceived physical health. Models were adjusted for demographic covariates previously identified as potential risk factors for depression.

Results

AYA survivors had higher prevalence of depression as compared to their caregivers (26.3% vs 18.7%, respectively). Survivors were 52.5% female, while caregivers were 94.2% female. Overall, ITR, treatment modalities, and late effect risks were not statistically significant predictors of depression in either cohort, except for lower odds of depression for survivors at risk for cardiac problems. Still, aspects of treatment like having a relapse and having surgery were positively associated with depression in both survivors and their caregivers in full logistic models. Not having private insurance was significantly associated with increased odds of depression in survivors in all models. Worse perceived health was negatively associated with depression in survivors and parents.

Conclusion

Future mental health care for cancer survivors should focus on individuals with inadequate health care coverage as a group with a particularly elevated risk for depression. Parents should also be included in the screening process for depression as their child transitions to adult survivorship.

Introduction

Although cancer continues to be a leading cause of chronic disease in children in the United States, mortality has decreased from 1970 to 2020 from 6.3 to 1.9 per 100,000 in children, and from 7.2 to 2.6 per 100,000 among adolescents. This translates to overall reductions of 70% and 64%, respectively over this 50-year time span.[1] Globally, the overall trend over the past 30 years suggests a decrease in mortality for childhood cancers.[4-7] Despite these mortality decreases, the long-term impact of pediatric cancer remain. These impacts vary, but can include a range of effects including: growth and development, organ functioning, reproductive capacity, risk of subsequent carcinogenesis and chronic conditions, and mental health impacts such as anxiety, fatigue, and other cognitive deficits.[8-18] The risk of late effects from pediatric cancer is a function of the type of cancer and its treatment, location of the cancer, age during treatment, overall health prior to diagnosis, and genetic makeup, and a myriad of factors impacting livelihood and quality of life for survivors of pediatric cancers.[19-25] Although childhood cancer leaves a myriad of challenges for the patient, the impact it has on the family is also glaring. This can vary from family functioning, marriage quality, parenting,[45] and even socio-economic implications.[60] Ultimately, a cancer diagnosis impacts not just the patient, but also the primary caregivers and family.

Psychosocial impacts of a cancer diagnosis can lead to long-lasting burdens for both survivors and their parental caregivers. Studies analyzing depression data from the Childhood Cancer Survival Study (CCSS) found survivors of pediatric cancer to have prevalence of depression ranging from 7-34.2%.[78,81-94] Identified risk factors for depression in survivors included younger age when beginning drinking,[81] loneliness,[94] chronic health conditions,[84] and less physical activity.[90]

Caregivers also faced elevated levels of depression when caring for pediatric cancer patients and survivors. Reported prevalence estimates ranged from 7.4% to 59.7% of any level of depression, including borderline depression.[125,128,130-133] Mothers were found to have a greater risk for depression.[132] Other risk factors for caregivers included: late effects in survivors being associated with needing greater caregiver support.[131] Furthermore, Hispanic parents had significantly higher depression rates as compared to non-

Hispanic parents. Other risk factors included lower income, higher perceived stress, and lower rating on the children's psychosocial functioning scores.[125]

The International Guideline Harmonization Group (IGHG), an international multidisciplinary team, established a number of recommendations, among which is surveillance of all survivors of childhood cancers for mental health outcomes, including depression. They highlighted a number of risk factors for depression among survivors. Although the strength of risk factors varies, they include a range of clinical, demographic, or treatment-related risk factors. Clinical risk factors include late effects/poor perceived health status, pain, early drinking behaviors, and decreased physical activity. Demographic risk factors include female sex, lower educational achievement, unemployment, marital status, and lower annual income. Treatment related risk factors include receiving chemotherapy, radiation, bone marrow transplant, or surgery, and having a relapse.[29]

This study aims to investigate how certain aspects of an Adolescent and Young Adult (AYA) survivor's cancer treatment may relate to depression in both the survivor as well as their parental caregivers. Since these AYA can experience a range of challenges in survivorhood, it is particularly important to understand correlates of depression in this group. Ultimately, the need for surveilling to better identify those survivors most at risk for depression is of great need, as recommended by the IGHG.[29] Some researchers argue that including the caregiver in addressing mental health outcomes may prove necessary, too.[127,141] This analysis will aim to identify both the survivors and their caregivers that may require greater attention for depression outcomes as they transition into survivorship.

Methods

Study Design

Data for this study was part of a larger, cross-sectional study, entitled *Predicting Childhood Cancer Survivors' Transition Readiness & Transfer Outcomes (SURV Transfer Outcomes)*. Principal Investigator at Emory University and the Children's Healthcare of Atlanta (CHOA), Dr. Jordan Gilleland Marchak, and Co-Investigator Dr. Ann Mertens, collected data from two cohorts of 18- to 25-year-olds childhood cancer survivors and their parents. The first aim focused on predictors of readiness to transition from pediatric to adult care among the cohort still engaged in pediatric survivor care, while the second aim focused on those who have transferred out of pediatrics and the predictors of adhering to adult survivor-focused healthcare. The study was approved by Institutional Review Boards at Emory University and CHOA. Data was collected from February 2017 to August 2019. Data from this study was used for an ancillary analysis to assess the relationship between a range of treatment-related indicators, including Intensity of Treatment (ITR), treatment modalities, late effects, and perceived health and depression in both AYA survivors of pediatric cancers and their caregivers.

Study Participants

Eligibility

Survivors and their parents were recruited through the Cancer Survivor Program (CSP) at the Aflac Cancer & Blood Disorders Center at CHOA. Patients were identified through the CSP's clinical databases. Inclusion criteria included: survivors aged 18-25, diagnosed with cancer ≤ 18 years old, ≥ 2 years since their most recent treatment, and having been seen at the Aflac CSP at least once in the previous 2 years (for Aim 1), or having transitioned out of the Aflac CSP to adult survivor care since 2013 (for Aim 2). Exclusion criteria included those patients that were non-English speaking. Since this ancillary analysis did not focus on healthcare transition, both cohorts were combined for the purpose of this analysis. Inclusion in this analysis were any participants (survivors or parents) that had completed data for the depression outcome, previous cancer treatment variables, and all covariates.

Recruitment

Potential participants were screened from the CSP database for eligibility. Following an initial letter describing the study being mailed, patients were contacted via phone and/or email for recruitment purposes. The consent process was completed online prior to the electronic administration of any study questionnaires. Consent information was presented electronically in the Research Electronic Data Capture

(REDCap) platform. Participants had to acknowledge receipt and understanding of participation prior to beginning the survey. Since all patients were AYA survivors, no minors were included in this study.

All components of the survey were completed electronically using REDCap. Unique participant identification numbers were assigned to all participants to ensure confidentiality of all patient data. Medical records from CHOA were also abstracted and included for relevant clinical data.

Study sample

The study included 481 enrolled participants (156 AYA-parent dyads, 95 AYA only, 74 parent only), totaling 251 AYA and 230 parent respondents. Of the 481 eligible parents and AYA, 4 participants were excluded due to missing data for the depression outcome variable. Of the remaining 477 eligible participants, 7 were removed based on missing depression risk factors. Of the 470 remaining, all other participants were removed due to having any missing or extraneous covariate data. The final analytic sample included 315 participants: 160 AYA and 155 parents that had no missing data for depression, risk factors, or covariates included in the model building (Figure 1).

Data Collection

The purpose of this analysis is to assess the association between previous cancer treatment and depression in pediatric survivors and parents. In this analysis, the main exposure variable, previous cancer treatment, was operationalized in three different ways: 1) via the ITR score, 2) via a set of variables related to treatment modalities, and 3) via the combination of risk for late effects and perceived health status. All study variables are described below.

Depression

Survivor and caregiver depression levels were assessed using the Patient-Reported Outcome Measure Information System (PROMIS) Depression v1 8a scale,[142,143] which has previously been validated in the literature.[144,145] It assesses self-reported depression symptoms through eight questions. Questions reflect negative mood, views of self, and social cognition, as well as decreased positive affect and engagement. This measure is not disease specific, so it can be more applicable to a wide range of patient populations. All questions reflect responses over the previous seven days. For each question, scores range from 1 (never) to 5 (always). Total depression scores are calculated by the cumulative sum of the eight questions and converted to T-scores (with a mean of 50 and standard deviation of 10, standardized to the general US population). Higher scores indicated greater depressive symptoms.[146] Based on T-scores, severity of depression is assessed as follows: none to slight depression (scores >55), mild depression (scores from 55 to 59.9), moderate depression (scores from 60 to 69.9), and severe depression (scores ≥ 70).[146] In the current analysis, we opted to dichotomize depression where all scores greater than 55 were recategorized as having depression, and those below 55 were categorized as no depression.

Intensity of Treatment (ITR)

This ITR-3 scale was used to assess the intensity of treatment exposures among childhood cancer survivors. Using a clinically based and validated assessment tool,[147,148] pediatric oncologists can categorize the intensity of pediatric treatments for their patients using information from the medical record. Scores range from Level 1 to Level 4, with 1 being the least intense, and 4 being the most intense. Factors contributing to this score include: diagnosis type, stage, and treatment modalities (history of relapse, and receipt of chemotherapy, surgery, radiation, or transplant). Clinical data needed to generate ITR scores were abstracted from survivor medical records.

Treatment modalities

The treatment modalities included: whether the patient experienced a relapse, had a secondary malignancy, had chemotherapy, had radiation, had a bone marrow transplant (BMT), or had a surgery. These data were abstracted from survivor medical records and were reported as binary yes/no variables.

Risk of Late Effects and Perceived Health Status

Late effect risks due to treatment exposures

Late effects of treatment exposures included the risk for: a secondary cancer, fertility problems, cardiac problems, or learning/memory/attention (neurocognitive) problems. These risks were assessed as outlined in the Children's Oncology Group's Long-Term Follow-Up Guidelines for Survivors of

Childhood, Adolescent, and Young Adult Cancers Version 5.0.[149] Specific treatment exposures confer risk for each of these late-effects, including cumulative dosing of certain chemotherapies, radiation exposure and dosing to specific fields, or specified surgeries. Other impacts on fertility and neurocognitive late effects include age at diagnosis, while genetic makeup can also impact fertility problems.[149] Data were abstracted from survivor medical records and each risk was assessed as a binary yes/no variable.

Perceived Health Status

Perceived health status was assessed using the Global Health PROMIS measure, v1.1.[150] Perceived health was collected at both the patient and parent level via a self-reported questionnaire similar to the depression instrument. This tool assesses an individual's physical, mental, and social health and is not disease specific. Across 10 questions, the measure produces two scores: Physical Health and Mental Health. Only the Physical Health score (a composite of 4 of the 10 questions) was included for the purpose of ascertaining a physical health score that would serve as a proxy for perceived physical health in both survivors and their parents. For scoring feasibility, the scores were first converted to the more recently available version 1.2. Similar to the depression scoring, the raw scores were converted to T-scores with a mean of 50 and a standard deviation of 10. Scores ranged from 16.2 to 67.7. Upon converting to T-scores, scores were categorized into 5 unique groups to describe physical health of the respondents: poor (below 35), fair (35-41.9), good (42-49.9), very good (50-57.9), and excellent (above 58).[150]

Demographic and socioeconomic covariates

Demographic and socioeconomic variables were collected for all survivors and parents and were self-reported. For survivors, covariates included were race, sex, and insurance status. For the purposes of having sufficient numbers for analyses, racial categories were collapsed into a binary *white* versus *non-white* variable. Similarly for insurance status, this variable was collapsed down into *private-insurance* versus *non-private*, which included all survivors with Medicaid, uninsured, or that listed 'other' as their insurance.

For parents, covariates included in this analysis were race, family income, education status, and employment status. Family income categorization was recategorized into a low, medium, high, and unknown categories based on estimated family yearly income.

Data analysis

Analyses were conducted separately for each cohort (survivors vs. parents). Descriptive statistics were performed to assess the severity of depression (on the categorical and continuous scales) and evaluate the distribution of ITR, treatment modalities, late effects, perceived health, and demographic risk factors. Proportions were used for categorical variables and means (standard deviations) or medians (interquartile ranges) were used for continuous variable. Differences in treatment-related variables and other risk factors between individuals with and without depression were compared using unadjusted logistic regression models.

Logistic regression was used to assess the association between the main exposure variable, previous cancer treatment, and the dichotomous depression measure. The main exposure was evaluated in three different ways, via: 1) the ITR score (reference group = “Less Intensive,” which was a combination of both “Least Intensive” and “Moderately Intensive” scores based on low numbers in both cohorts in these respective categories); 2) the set of variables related to treatment modalities (reference group = “No” for all variables); 3) the combination of risk for late effects (reference group = “No” for all variables) and survivor perceived health status (reference group = “Poor/Fair,” which is a combination of the “Poor” and “Fair” scores based on low numbers in both cohorts in these respective categories). Three unique models were built for each cohort (survivors and parents), focusing on each of the exposure groups: ITR, treatment modalities, and late effects and perceived health of the survivor.

A univariate model was performed followed by an adjusted model that controlled for the following sets of covariates: for survivors (sex, race, insurance status) and for parents (race, education, family income, employment status, and parental perceived health). Parental perceived health was recoded as a binary outcome of “Poor/Fair/Good” and “Very Good/Excellent” due to low responses in categories for the parents. For the late effects and perceived health model in caregivers, the parent's perceived health score was also adjusted for. Covariates were selected for inclusion in the full model based on evidence of being risk factors for depression. Variables with a high percentage of missing data were excluded from analysis. Regarding treatment modalities, categories of secondary malignancies and chemotherapies were excluded from models for both cohorts due to low responses in certain categories to this question. For late effect risks, the question about risk for secondary cancers was also excluded from models for both cohorts for the same reason. Odds ratios and 95% confidence intervals were calculated and used to estimate the strength and statistical significance of the associations. The level of statistical significance was set at 0.05 for all analyses. Statistical Analysis System (SAS) 9.4 (SAS Institute, Cary, NC) was used for analysis.

Results

Descriptive Data

A total of 315 respondents were included in this analysis: 160 survivors and 155 parents of survivors. There were 105 dyads, 55 survivor-only, and 50 parent-only participants that were included in the sample. All demographics and risk factors are reported in Table 1. Average age of the Adolescent and Young Adult (AYA) survivor population was 19.6 (SD=1.8), while parent average age was 48.9 (SD=5.6). Survivors had slightly more females (52.5%) as compared to males, while parents were predominantly female (94.2%). As it pertains to the depression outcome, 26.2% of survivors had any level of depression according to the PROMIS measure, compared to 18.7% of parents. To break the depression outcome down further, 12.5% of survivors had mild depression, 11.2% had moderate, and 2.5% had severe. As it pertains to parents, 13.6% had mild depression, while 5.2% had moderate depression and none reported severe depression (Table 1).

Regarding clinical data on survivors, among the types of cancers diagnosed in the survivor cohort, leukemia was the most common (40.6%), followed by sarcomas (18.1%), non-Hodgkin lymphoma (10.6%), and then Hodgkin Lymphoma (9.4%). Similar patterns were observed in the parent cohort as well. As for treatment intensity, among survivors the most common level of ITR was *very intense* (38.8%), followed by *moderately intense* (33.75%) and *most intense* (25.63%). Only 1.88% of survivors had the *least intensive* level. There were similar percentages among children in the parents cohort, with a greater percentage having the *very intensive* category at 44.52% (Table 2).

Regarding treatment modalities, 12.5% of survivors experienced a relapse, while only 1.88% experienced a second malignancy. A majority of patients had chemotherapy (98.8%), while 35% had radiation and 17.5% had a bone marrow transplant (BMT). Over a third of survivors (35.6%) had surgery as part of treatment. For late effect risk factors based on clinical records, 93.1% of survivors were reported at risk for a secondary cancer, 88.8% at risk for fertility problems, 86.3% at risk for cardiac problems, and 60% at risk for neurocognitive problems. Similar patterns were observed in the parent cohort as well (Table 2).

In terms of perceived health status based on the PROMIS Global Physical health score, both survivors and their parents completed physical health scores for their own respective perceived physical health. For survivors, 45.6% had a *very good* physical score, while 54.2% of parents had a *very good score*. For a *good score,* 25.6% of survivors had this score, while 22.6% of parents had this score. For an *excellent* score, 19.4% of survivors had this score, while 13.6% of parents did. For *fair* scores, 7.5% of survivors had this score, and 5.8% of parents did. Only 1.9% of survivors scored *poor*, while 3.9% of parents had this score (Table 2).

Association of cancer treatment-related variables and depression in survivors

Intensity of Treatment

The first logistic regression model for depression in survivors assessed associations of ITR categories with depression. Both unadjusted and adjusted models did not show an association between ITR levels and depression among survivors when comparing to *less intensive* ITR (AOR for *very intensive* = 0.9 (95% CI: 0.4-2.2), AOR for *most intensive* = 1.0 (95% CI: 0.4-2.7)). Of the demographic variables adjusted for, only insurance was associated with the outcome. Those without private insurance (including Medicaid, uninsured, and other) were 3.3 times more likely to have diagnosed depression compared to those with private insurance (AOR=3.3, 95% CI: 1.5-6.9) when controlling for other covariates and ITR. Females had lower odds of depression compared to males after controlling for other covariates and ITR, but this was not statistically significant (AOR= 0.6, 95% CI: 0.3-1.2). Non-white participants had slightly lower odds of depression in the full model, but this was also not statistically significant (AOR = 0.9, 95% CI: 0.4-2.1) when controlling for ITR and other covariates. (Table 3a).

Treatment Modalities

The second model analyzed four aspects of cancer treatment (whether or not the patient experienced a relapse, radiation, BMT, or surgery) and their association with depression in survivors. Secondary malignancy and chemotherapy were not included in this model due to insufficient number of responses for categories in these questions. In both unadjusted and adjusted models, survivors who experienced a relapse (AOR = 1.6, 95% CI: 0.4-5.8), radiation (AOR = 1.3, 95% CI: 0.5-3.3), or surgery (AOR= 1.3, 95% CI: 0.6-3.0) all had greater odds of depression compared to survivors who did not experience these treatment modalities, but none of these were statistically significant. Those who had a BMT had lower odds of depression (AOR = 0.7, 95% CI: 0.2-2.2) in both models, but this was also not significant. Similar to the previous model, patients with non-private insurance had greater odds of depression after controlling for all treatment modalities and demographic risk factors (AOR = 3.4, 95% CI: 1.6-7-7.4) (Table 3b).

Late effects and perceived health status

The third logistic regression model analyzed potential risk for late effects of cancer treatment (whether or not the survivor was at risk for fertility, cardiac, or neurocognitive problems) as well as perceived health status (based on the Global Health PROMIS perceived health measure), and their association with depression in survivors. Risk for secondary malignancies was not included in this model due to insufficient number of responses for categories in this question. As it pertains to late effect risks, survivors at risk for infertility (AOR = 3.2, 95% CI: 0.8-12.4) and neurocognitive problems (AOR = 1.1, 95% CI: 0.5-2.5) had greater odds of depression as compared to those not at risk in both unadjusted and adjusted models, but none of these associations were statistically significant. On the other hand, patients at risk for cardiac problems had lower odds of depression compared to those not at risk for cardiac problems (AOR = 0.2, 95% CI: 0.03-0.9) in both unadjusted and adjusted models. This was statistically significant. (Table 3c).

As it pertains to perceived physical health, when comparing to those who scored in the *poor/fair* category, all other groups (categorized as *good*, *very good*, *and excellent*) had greater odds of depression in both unadjusted and adjusted models. Those in the *very good* (AOR = 4.5, 95% CI: 1.3-16.2) and the *excellent* (AOR = 17.8, 95% CI: 2.7-116.3) categories had significant associations with depression in both models. Lastly, insurance status remained associated with depression in survivors in the fully adjusted model (AOR = 2.7 95% CI: 1.2-6.3) (Table 3c).

Modeling predictors of depression for parents

Intensity of Treatment

The first model for depression in parents investigated how the child survivor's ITR affects their parent's depression, before and after controlling for demographic covariates (family income, education, employment status, race) and parent's perceived health. Both unadjusted and adjusted models of ITR showed lower odds of depression in the *most intensive* (AOR = 0.6, 95% CI: 0.2-1.8), but no association in the *very intensive* (AOR = 1.0, 95% CI: 0.4-2.8) treatment groups when compared to the *less intensive* group. Neither of those associations were statistically significant. As it pertains to other demographic covariates, those with higher income had greater odds of depression in both models when compared to those with less than $50,000 annual family income. These were not significant associations for those with a medium income (AOR = 1.7, 95% CI: 0.6-5.3) or a high income (AOR = 1.3, 95% CI: 0.4-4.6). Higher education in the full model was associated with lower odds of depression when compared to those that were a high school graduate, but this was not significant for any college (AOR = 0.7, 95% CI: 0.2-2.2) or graduate degree or higher (AOR = 0.9, 95% CI: 0.2-4.3). On the other hand, parents who scored *very good/excellent* on the PROMIS perceived physical health score had greater odds of depression as compared to those who scored *poor/fair/good* (AOR = 3.6, 95% CI: 1.4-9.4), and this was statistically significant in fully adjusted models. (Table 4a).

Treatment Modalities

The second model analyzed four aspects of the survivor's cancer treatment (whether or not the patient had a relapse, radiation, BMT, or surgery) and their ability to predict depression in parents. Secondary malignancy and chemotherapy were not included in this model due to insufficient number of responses for categories in these questions. Parents whose children experienced a relapse (AOR = 1.3, 95% CI: 0.4-5.0) or surgery (AOR = 1.8, 95% CI: 0.6-4.9) in adjusted models had greater odds of depression, but neither of these were significant associations. Parents whose children experienced radiation (AOR = 0.7, 95% CI: 0.2-1.8) or had a BMT (AOR = 0.4, 95% CI: 0.1-1.5) had lower odds of depression in both unadjusted and fully adjusted models, but neither of these associations were not statistically significant. Again, parents who scored *very good/excellent* on the PROMIS perceived physical health score had greater odds of depression as compared to those who scored *poor/fair/good* (AOR = 3.8, 95% CI: 1.4-10.3), and this was statistically significant in fully adjusted models (Table 4b).

Late effects and perceived health status

The third logistic regression model analyzed survivor's potential risk for late effects of cancer treatment (whether or not the survivor is at risk for fertility, cardiac, or neurocognitive problems) and the survivor's perceived health status (based on the Global Health PROMIS perceived health measure) and their ability to predict depression in parents. Risk for secondary malignancies was not included in this model due to insufficient number of responses for categories in this question. In both unadjusted and adjusted models, parents whose child was at risk for fertility (AOR = 0.4, 95% CI: 0.04-4.2), cardiac (AOR = 0.7, 95% CI: 0.1-4.7), or neurocognitive (AOR = 0.5, 95% CI: 0.2-1.7) problems had lower odds of depression compared to parents whose children were not at risk for these late effects. These were not statistically significant associations. Again, parents who scored *very good/excellent* on the PROMIS perceived physical health score had greater odds of depression as compared to those who scored *poor/fair/good* (AOR = 8.1, 95% CI: 0.6-105.1), but this was statistically significant in fully adjusted models (Table 4c).

When measuring the survivor's perceived physical health, parents whose child scored *very good/excellent* on the Global Health PROMIS measure had lower odds of depression in fully adjusted models when compared to parents whose children scored *poor/fair/good* (AOR = 0.3, 95% CI: 0.03-3.9). This association was not statistically significant (Table 4c).

Discussion

Summary of findings

This analysis assessed components of prior cancer treatment in AYA survivors and their impact on depression in survivors as well as their parental caregivers. Specifically, we evaluated the intensity of cancer treatment, the combination of treatment modalities received, and risk of late effects resulting from treatment combined with perceived physical health. While these factors have been identified in the literature,[29] this study was a comprehensive evaluation of these three assessments of risk factors for depression in both AYA survivors and their caregivers.

Overall, depression was higher in AYA survivors as compared to parents. Although the prevalence of depression in survivors is high, it is consistent with other findings for AYA survivors ranging from 2% to 40%.[78,81-85,87,88,90-94,96,117,118,120-122,134] On the other hand, parental depression was higher than the majority of studies that investigated prevalence in parental caregivers of AYA survivors,[125,128,131-134] aside from one study that found 36.3% of parents had borderline depression and 23.4% had identified levels of depression.[130] Ultimately, our study observed a high burden of depression in both cohorts, with survivors being particularly vulnerable.

Prior clinical evidence highlighted the myriad ways that a pediatric cancer diagnosis can impact both the patient,[8-25] as well as the family.[45-71] Findings from this study confirm prior findings that certain treatment modalities increased the odds of depression . Specifically, those who had a relapse, radiation, or surgery had greater odds of depression, as compared to patients without these treatments, but these were not statistically significant associations. Furthermore, survivors with risks for late effects on fertility and neurocognitive function had greater odds of depression in full logistic models as compared to survivors without those risks. None of these were significant associations. Yet, they highlight the impact treatment modalities and potential late risks can have on survivors. Interestingly though, survivors with risk for cardiac late effects had lower odds of depression than those without those risks. This association was statistically significant in full models. Although this contradicts the existing literature,[84] it is difficult to ascertain why this cohort had lower odds. Future research should investigate the avenues those with lower levels of depression are taking to mitigate depression symptoms.

Surprisingly, we anticipated that better perceived physical health would be associated with lower odds of depression in survivors. Instead, findings showed significant associations for lower odds of depression in those with worse perceived health. These findings, while significant, contradict the existing body of work that details the opposite association.[29] Still, this validated measure assessing physical health showed a negative association with depression. Future research should investigate this association further with other samples of similar cohorts.

Of the range of demographic and socioeconomic factors evaluated, lack of private insurance was significantly associated with depression in survivors. This association highlights the important role that having private insurance may have in mitigating depression in survivors. As there is a dearth of mental health providers nationwide, exacerbated by the Covid-19 pandemic,[151-154] access to mental health services is even further limited for those without private insurance.[155-157] Overall, these findings highlight the important role that insurance may play in mitigating depression levels. Although this study did not assess whether participants were actively seeing a clinician for their mental health, these associations still offer insight into the impact that insurance may play in the odds of depression in AYA survivors.

Lastly, regarding parental caregivers, similar findings were reported regarding treatment modalities of their AYA survivors – parents whose AYA survivors had a history of a relapse or surgery had greater odds of depression in fully adjusted models. Although these were not significant associations, they still highlight the impact a child's cancer diagnosis can have on a parent's overall wellbeing, even after the completion of treatment. These findings emphasize the impact of treatments on caregiver wellbeing, too. All parents whose AYA survivors had risk for fertility, cardiac, or neurocognitive problems in fully adjusted models had lower odds of depression. Despite these findings not being significant, these data are important to consider in light of the impact long-term health outcomes may have on parents whose children are survivors of pediatric cancers. Since parents had lower rates of depression compared to the AYA survivors, this may be one potential avenue for why this contradicted our initial hypotheses. Still, more research is required to confirm why parents whose children had these late-effect risks had lower odds of depression compared to those without these risks.

Strengths and limitations

This ancillary analysis was unique in its approach of considering how AYA survivor's treatment can also impact depression in their parental caregivers. By constructing this analysis to have three models for each cohort, we could more accurately assess whether similar risk factors for depression in AYA survivors (previously identified in the literature and also assessed here) may also predict depression in their caregivers. Furthermore, this study was novel in that it investigated cancer-related aspects of treatment separately in each of the models. Since the cancer experience is truly one that parents have an active role in, the analysis attempted to assess whether those aspects of treatment that may impact depression in the survivor may also be associated with depression in their parents, too. Second, this analysis included a comprehensive assessment of self-reported and medically abstracted data that may ultimately impact depression in these cohorts. Due to the breadth of data in the larger study, this secondary analysis was able to include a number of self-reported measures that have been previously validated in the literature.

Limitations should also be considered in the context of this analysis. First, this was cross-sectional study, so causal inferences should not be inferred based on these findings. Second, a number of important variables could not be included in logistic model building due to low numbers, like sex for the parent cohort. In addition, a number of risk factors were excluded from the models due to small numbers for certain responses; including use of chemotherapy, secondary cancers, and being at risk for a secondary malignancy.

Findings thereby should not be generalized to other cohorts as some risk factors for depression could not be included. Third, there were no brain tumor survivors included in this analysis. Previously literature has highlighted the dearth of research on mental health outcomes in pediatric brain tumor survivors.[19] Future research should include cohorts of these patients as prior evidence has shown they may face greater prevalence of depression as compared to AYA survivors of other types of cancers.[17,98-104]

Future recommendations

This study found high prevalence of depression in AYA survivors of pediatric cancers as well as their parental caregivers. There is a need to focus greater efforts on mitigating these high rates of depression among these AYA survivors. Specifically, particular attention should be paid to vulnerable populations who may not have access to mental health services. Future efforts should incentivize making these services more accessible to survivors who are more at risk. Challenges to mitigating these disparities in mental health coverage remain for those with limited access to quality health coverage. It is important to acknowledge that mental health services are often hard to access, even for those who have greater health insurance coverage. Still, normalizing these discussions around mental health during treatment can help to increase the likelihood of survivors to continue this treatment trajectory as they transition to adult survivorship.

Guidelines from the IGHG recommend surveillance of AYA survivors for a myriad of mental health outcomes.[29] The benefits to maintaining these screenings can help to track survivors that may no longer be actively in clinic as they transition into survivorship. Furthermore, increased focus should also attempt to maintain active dialogue with parental caregivers who may also still face lasting impacts of their child's cancer diagnosis. Lastly, the findings of this analysis reflect a mixed consensus with previously recognized risk factors for depression in survivors. Ultimately, these aspects of cancer treatments must continue to be surveilled as they may help to identify those survivors most at risk for depression in survivorship. By increasing these conversations early on in the treatment process, the goal of increased mental health surveillance in survivorship for AYA and their caregivers can potentially lead to decreased prevalence of depression in these cohorts that are at increased risk for it.

Tables and Figures

Figure 1: Diagram of Analytic sample

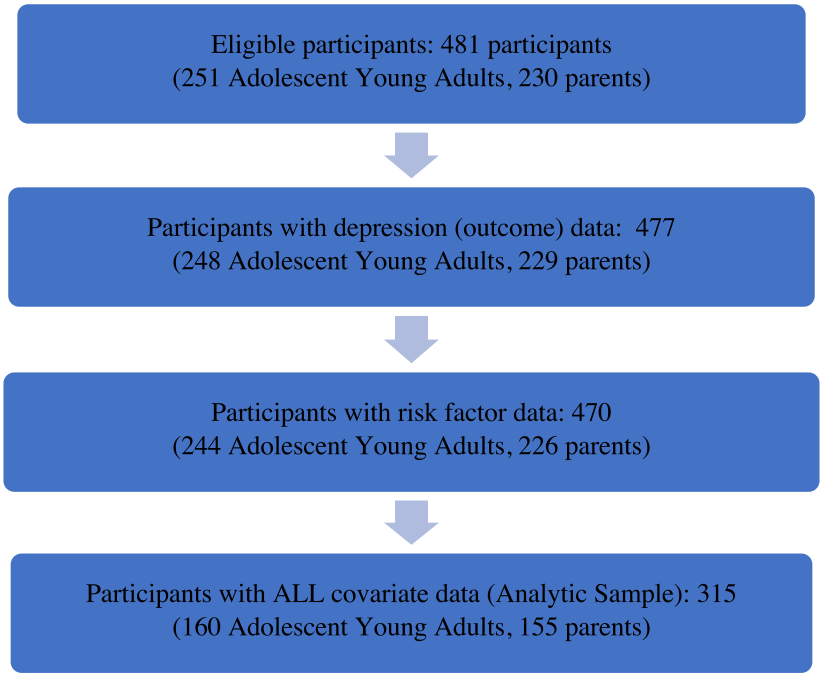

Table 1: Demographic, socioeconomic, and self-reported measures among pediatric cancer survivors and their caregivers

Variable	Survivors N= 160	Parents N= 155
Age – mean (SD)*	19.6 (1.8)	48.9 (5.6)
Sex – N (%)		
Male	76 (47.5)	9 (5.8)
Female	84 (52.5)	146 (94.2)
White	114 (71.3)	114 (73.6)
African American	30 (18.8)	28 (18.1)
Asian	4 (2.5)	5 (3.2)
Other	12 (7.5)	8 (5.2)
Ethnicity		
Hispanic	14 (8.8)	9 (5.8)
Not Hispanic	146 (91.3)	146 (94.2)
Type of health insurance		
Private	108 (67.5)	n/a
Medicaid	27 (16.9)	n/a
None	6 (3.8)	n/a
Other	19 (11.9)	n/a
Education Level (survivors)		
High school graduate or less	82 (51.3)	n/a
Any college	78 (48.8)	n/a
Education Level (parents)		
High school graduate or less	n/a	26 (16.8)
Any college	n/a	98 (63.2)
Graduate degree or higher	n/a	31 (20.0)
Employment		
Yes	89 (55.6)	114 (73.6)
No	71 (44.4)	41 (26.45)
Family Income		
Low (>$9,999 to $49,999)	33 (20.6)	38 (24.5)
Medium ($50,000 to $99,999)	34 (21.3)	49 (31.6)
High (>$100,000)	43 (26.9)	55 (35.5)
Unknown	50 (31.3)	13 (8.4)
Perceived Physical Health [Global Physical Health (PROMIS)]**		
Poor	3 (1.9)	6 (3.9)
Fair	12 (7.5)	9 (5.8)
Good	41 (25.6)	35 (22.6)
Very Good	73 (45.6)	84 (54.2)
Excellent	31 (19.4)	21 (13.6)
Depression- median (IQR)	44.7 (16.9)	44.7 (13.9)
Depression (Binary) N (%)		
Yes	42 (26.3)	29 (18.7)
No	118 (73.8)	126 (81.3)
Depression (Categorical) N (%)		
None	118 (73.8)	126 (81.3)
Mild	20 (12.5)	21 (13.6)
Moderate	18 (11.3)	8 (5.2)
Severe	4 (2.5)	0

* SD= Standard Deviation

** Perceived physical health is a self-reported PROMIS measure that both the survivor and parents completed on their own perceived physical health

Table 2: Cancer related variables for pediatric patients, reportedly separately for the survivor and parent study cohorts

	Survivors	Parents*
Variable	N (%)	N (%)
Diagnosis Category		
Leukemia	65 (40.6)	59 (38.1)
Hodgkin Lymphoma	15 (9.4)	13 (8.4)
Non-Hodgkin Lymphoma	17 (10.6)	16 (10.3)
Kidney tumors	8 (5.0)	11 (7.1)
Neuroblastoma	14 (8.8)	10 (6.5)
Sarcomas	29 (18.1)	29 (18.7)
Other	12 (7.5)	17 (11.0)
Treatment Intensity (%)		
Least intensive	3 (1.9)	4 (2.6)
Moderately intensive	54 (33.8)	50 (32.3)
Very intensive	62 (38.8)	69 (44.5)
Most intensive	41 (25.6)	32 (20.7)
Did patient experience a relapse?		
Yes	20 (12.5)	20 (12.9)
No	140 (87.5)	135 (87.1)
Did patient experience a secondary malignancy?		
Yes	3 (1.9)	3 (1.9)
No	157 (98.1)	152 (98.1)
Did patient have chemotherapy?		
Yes	158 (98.8)	152 (98.1)
No	2 (1.3)	3 (1.9)
Did patient have radiation?		
Yes	56 (35.0)	48 (31.0)
No	104 (65.0)	107 (69.0)
Did patient have a bone marrow transplant?		
Yes	28 (17.5)	24 (15.5)
No	132 (82.5)	131 (84.5)
Did patient have surgery?		
Yes	57 (35.6)	57 (63.2)
No	103 (64.4)	98 (36.8)
Is patient at risk for a secondary cancer?		
Yes	149 (93.1)	147 (94.8)
No	11 (6.9)	8 (5.2)
Is patient at risk for fertility problems		
Yes	142 (88.8)	138 (89.0)
No	18 (11.3)	17 (11.0)
Is patient at risk for cardiac problems?		
Yes	138 (86.3)	132 (85.2)
No	22 (13.8)	23 (14.8)
Is patient at risk for learning, memory, or attention problems (neurocognitive)?		
Yes	96 (60.0)	91 (58.7)
No	64 (40.0)	64 (41.3)

* All responses for parents are assigned based on their respective child/survivor's medical records

Table 3a: Association of Intensity of Treatment with depression in survivors

Variable	Unadjusted OR (95% CI)*	Adjusted OR (95% CI)*
Treatment Intensity		
Less intensive	REF	REF
Very intensive	0.9 (0.4, 2.0)	0.9 (0.4, 2.2)
Most intensive	0.9 (0.4, 2.2)	1.0 (0.4, 2.7)
Sex		
Male	---	REF
Female	---	0.6 (0.3, 1.2)
Type of health insurance		
Private	---	REF
Non-private***	---	3.3 (1.5, 6.9)**
Race		
White	---	REF
Non-white	---	0.9 (0.4, 2.1)

* OR= Odds Ratio, CI= Confidence Interval

** Statistically significant associations

*** Non-private includes those that listed *Medicaid*, *Other*, or *No insurance*

Table 3b: Association of Treatment Modalities with depression in survivors

Variable	Unadjusted OR (95% CI)*	Adjusted OR (95% CI)*
Did patient experience a relapse?		
No	REF	REF
Yes	1.5 (0.5, 4.7)	1.6 (0.4, 5.8)
Did patient have radiation?		
No	REF	REF
Yes	1.3 (0.6, 2.7)	1.3 (0.5, 3.3)
Did patient have a bone marrow transplant?		
No	REF	REF
Yes	0.9 (0.4, 2.2)	0.7 (0.2, 2.2)
Did patient have surgery?		
No	REF	REF
Yes	1.3 (0.6, 2.)	1.3 (0.6, 3.0)
Sex		
Male	---	REF
Female	---	0.7 (0.3, 1.4)
Type of health insurance		
Private	---	REF
Non-private***	---	3.4 (1.6, 7.4)**
Race		
White	---	REF
Non-white	---	0.9 (0.402, 2.108)

* OR= Odds Ratio, CI= Confidence Interval

** Statistically significant associations

*** Non-private includes those that listed *Medicaid*, *Public*, and *No insurance*

Table 3c: Association of late effect and perceived health status with depression in survivors

Variable	Unadjusted OR (95% CI)*	Adjusted OR (95% CI)*
Is patient at risk for fertility problems?		
No	REF	REF
Yes	1.9 (0.7, 5.4)	3.2 (0.8, 12.4)
Is patient at risk for cardiac problems?		
No	REF	REF
Yes	0.401 (0.1, 1.4)	0.2 (0.03, 0.9)*
Is patient at risk for learning, memory, or attention problems (neurocognitive)?		
No	REF	REF
Yes	1.2 (0.5, 2.1)	1.1 (0.5, 2.5)
Perceived Physical Health [Global Physical Health (PROMIS)]		
Poor/Fair	REF	REF
Good	1.3 (0.4, 4.3)	1.4 (0.4, 5.0)
Very Good	5.3 (1.6, 17.1)	4.5 (1.3, 16.2)**
Excellent	16.6 (2.9, 95.9)	17.8 (2.7, 116.3)**
Sex		
Male	---	REF
Female	---	0.8 (0.4, 1.8)
Type of health insurance		
Private	---	REF
Non-private***	---	2.7 (1.2, 6.3)**
Race		
White	---	REF
Non-white	---	0.9 (0.4, 2.1)

* OR= Odds Ratio, CI= Confidence Interval

** Statistically significant associations

*** Non-private includes those that listed *Medicaid*, *Public*, and *No insurance*

Table 4a: Association of Intensity of Treatment with depression in parents

Variable	Unadjusted OR (95% CI)*	Adjusted OR (95% CI)*
Treatment Intensity (Predictor)		
Less intensive	REF	REF
Very intensive	0.9 (0.4, 2.4)	1.0 (0.37, 2.8)
Most intensive	0.6 (0.2, 1.7)	0.6 (0.2, 1.8)
Family Income		
Low (>$9,999 to $49,999)	---	REF
Medium ($50,000 to $99,999)	---	1.7 (0.6, 5.3)
High (>$100,000)	---	1.3 (0.4, 4.6)
Unknown	---	2.4 (0.4, 13.8)
Education		
High school graduate or less	---	REF
Any college	---	0.7 (0.2, 2.2)
Graduate degree or higher	---	0.9 (0.2, 4.3)
Employment		
No	---	REF
Yes	---	1.4 (0.5, 3.7)
Race		
White	---	REF
Non-white	---	0.9 (0.3, 2.4)
Perceived Physical Health [Global Physical Health (PROMIS)] – Parent* **		
Poor/Fair/Good	---	REF
Very Good/Excellent	---	3.6 (1.4, 9.4) **

* OR= Odds Ratio, CI= Confidence Interval

** Statistically significant associations

*** For PROMIS scores, individual categories *poor, fair,* and *good* were collapsed into one category, while *very good* and *excellent* were collapsed into another due to small numbers in certain categories.

Table 4b: Association of treatment Modalities with depression in parents

Variable	Unadjusted OR (95% CI)*	Adjusted OR (95% CI)*
Did patient experience a relapse?		
No	REF	REF
Yes	0.6 (0.2, 2.0)	1.3 (0.4, 5.0)
Did patient have radiation?		
No	REF	REF
Yes	0.6 (0.2, 1.3)	0.7 (0.2, 1.8)
Did patient have a bone marrow transplant?		
No	REF	REF
Yes	0.5 (0.2, 1.3)	0.4 (0.1, 1.5)
Did patient have surgery?		
No	REF	REF
Yes	1.4 (0.6, 3.2)	1.8 (0.6, 4.9)
Family Income		
Low (>$9,999 to $49,999)	---	REF
Medium ($50,000 to $99,999)	---	2.3 (0.7, 7.7)
High (>$100,000)	---	1.4 (0.4, 5.1)
Unknown	---	2.8 (0.5, 16.9)
Education		
High school graduate or less	---	REF
Any college	---	0.6 (0.2, 2.0)
Graduate degree or higher	---	0.8 (0.2, 4.3)
Employment		
No	---	REF
Yes	---	1.4 (0.5, 3.9)
Race		
White	---	REF
Non-white	---	0.8 (0.3, 2.2)
Perceived Physical Health [Global Physical Health (PROMIS)] – Parent * **		
Poor/Fair/Good	---	REF
Very Good/Excellent	---	3.8 (1.4, 10.3)

* OR= Odds Ratio, CI= Confidence Interval

** Statistically significant associations

*** For PROMIS scores, individual categories *poor, fair,* and *good* were collapsed into one category, while *very good* and *excellent* were collapsed into another due to small numbers in certain categories.

Table 4c: Association of late effect risks and perceived health status with depression in parents

Variable	Unadjusted OR (95% CI)*	Adjusted OR (95% CI)*
Is patient at risk for fertility problems?		
No	REF	REF
Yes	0.5 (0.1, 2.5)	0.4 (0.04, 4.2)
Is patient at risk for cardiac problems?		
No	REF	REF
Yes	0.6 (0.2, 2.2)	0.7 (0.1, 4.7)
Is patient at risk for learning, memory, or attention problems (neurocognitive)?		
No	REF	REF
Yes	0.5 (0.2, 1.2)	0.5 (0.2, 1.7)
Perceived Physical Health [Global Physical Health (PROMIS)] – Survivor ***		
Poor/Fair/Good	---	REF
Very Good/Excellent	---	0.3 (0.03, 3.9)
Family Income		
Low (>$9,999 to $49,999)	---	REF
Medium ($50,000 to $99,999)	---	1.9 (0.5, 7.8)
High (>$100,000)	---	1.7 (0.4, 7.7)
Unknown	---	3.5 (0.3, 36.5)
Education		
High school graduate or less	---	REF
Any college	---	0.6 (0.1, 2.8)
Graduate degree or higher	---	0.7 (0.1, 5.1)
Employment		
No	---	REF
Yes	---	1.4 (0.4, 4.8)
Race		
White	---	REF
Non-white	---	1.4 (0.4, 5.3)
Perceived Physical Health [Global Physical Health (PROMIS)] – Parent ***		
Poor/Fair/Good	---	REF
Very Good/Excellent	---	8.1 (0.6, 105.1)

* OR= Odds Ratio, CI= Confidence Interval

** Statistically significant associations

*** For PROMIS scores, individual categories *poor, fair,* and *good* were collapsed into one category, while *very good* and *excellent* were collapsed into another due to small numbers in certain categories.

Chapter 4: Discussion

Significance of findings

The purpose of this analysis was to assess whether there were associations between aspects of previous cancer treatment for AYA survivors of pediatric cancer and depression, in both survivors and their parental caregivers. We anticipated finding associations in each of the three models (ITR, treatment modalities, and late effect risk factors and perceived physical health) as components of each of these have been previously identified in the literature as risk factors for depression in survivors.[29] Overall, depression was higher in AYA survivors (26.3%) as compared to their caregivers (18.7%). Although the prevalence of depression in survivors is high, it agrees with prior literature that finds depression ranges for AYA survivors ranging from 2% to 40%.[78,81-85,87,88,90-94,96,117,118,120-122,134] Furthermore, caregiver depression remained higher than a majority of studies that investigated prevalence in caregivers of AYA survivors,[125,128,131-134] aside from one study that found 36.3% of parents had borderline depression and 23.4% had identified levels of depression.[130] Ultimately, this sample faced a high burden of depression in both cohorts, of which survivors were particularly vulnerable for.

As it pertains to previously identified risk factors for depression, ITR, treatment modalities, nor late effect risk factors were significantly associated with depression in either cohort, except for being at risk for cardiac late effects in survivors. Still, it is important to highlight the role these aspects of cancer treatment play in the overall wellbeing of AYA survivors as they move further away from their diagnosis. Clinical evidence highlights the myriad ways that a pediatric cancer diagnosis can impact both the patient,[8-25] as well as the family.[45-71] Findings from this analysis concur that certain treatment modalities increased the odds of depression in full logistic models; survivors who had a relapse, radiation, or surgery had greater odds of depression, as compared to patients without these treatments. Although these were not significant associations, they still reflect the vital role that treatment modalities have in how AYAs move through survivorship long after treatment has concluded. Furthermore, patients with risks for late effects in fertility problems and neurocognitive problems had greater odds of depression in full logistic models as compared to patients without. These associations were not significant, but again highlight the impact of treatment in potential late risks survivors may endure later on in life, long after treatment has concluded.

Aside from cancer treatments and their associations with depression in survivors, is important to highlight the role that private insurance had in predicting depression in this cohort. In univariate and fully adjusted models, those without private insurance had significantly greater odds of depression as compared to those without private insurance. In this variable, the non-insurance cohort included those with *Medicaid*, those *uninsured*, and those that listed *other* for this survey question. The variable was collapsed due to low Ns in each category (see Table 1). Still, this strong association highlights the important role that having private insurance has in mitigating depression in survivors. There is a dearth of mental health providers nationwide, as proven by the Covid-19 pandemic.[151-154] Access to mental health services is even further limited for those without private insurance. Overall, these findings highlight the important role that insurance can play in mitigating depression levels.[155-157] Although this study did not assess whether participants were actively seeing a clinician for their mental health, these associations still offer insight into the impact that insurance may play in the odds of depression in AYA survivors.

As it pertains to associations with depression in parental caregivers, similar findings were reported regarding treatment modalities of their AYA survivors – parents whose AYA survivors had a history of a relapse or surgery had greater odds of depression in fully adjusted models. Although these were not significant associations, they still highlight the impact a child’s cancer diagnosis can have on a parent’s overall wellbeing, even after the completion of treatment. As previously mentioned, there are a plethora of ways in which parental caregivers can be impacted by a child’s cancer diagnosis. These findings agree with that consensus and emphasize the impact of treatments on their wellbeing, too. Interestingly though, the late effect risk factors for AYA survivors were negatively associated with depression in their parental caregivers. All parents whose AYA survivors had risk for fertility, cardiac, or neurocognitive problems in fully adjusted models had lower odds of depression. Despite these findings not being significant, these data are important to consider in light of the impact long-term health outcomes may have on parents whose children are survivors of pediatric cancers.

Strengths and Limitations

This investigation was an ancillary analysis of a larger study conducted by CHOA's CSP. Unique to this analysis was the approach of considering how AYA survivor's treatment can also impact depression in their parental caregivers. By constructing this analysis to have three models for each cohort, we could more accurately assess whether similar risk factors for depression in AYA survivors (previously identified in the literature and also assessed here) may also predict depression in their caregivers. Since the cancer experience is truly one that parental caregivers have an active role in, the analysis attempted to assess whether those aspects of treatment that may impact depression in the survivor may also be associated with depression in their parental caregivers.

Second, this analysis included a variety of self-reported and medically abstracted records that may ultimately impact depression in these cohorts. Due to the breadth of data in the larger study, this ancillary analysis was able to include a number of self-reported measures that have been previously validated in the literature. By using these measures to represent current physical health and depression levels, this analysis was able to more accurately depict how participants perceive their own physical and mental health at the time of survey completion.

Limitations should also be considered in the context of this analysis. First, this was cross-sectional study, so causal inferences should not be inferred based on these findings. Second, a number of variables could not be included in logistic model building due to low numbers; these included demographic covariates considered associated with depression, treatment modalities, and late effect risk factors. Therefore, findings should not be generalized to other cohorts as some important risk factors for depression had to be removed due to insufficient numbers. Third, a number of variables had to be recategorized in order to be included in this analysis. This was required due to having small numbers for individual responses within certain questions, like ITR and the Global Health PROMIS measure. Lastly, there were no brain tumor survivors included in this analysis. Previously literature has highlighted the dearth of research on mental health outcomes in pediatric brain tumor survivors.[19] Future research should include cohorts of these patients as prior evidence has shown they may face greater prevalence of depression as compared to AYA survivors of other types of cancers.[17,98-104]

Policy implications

This study found a high prevalence of depression in AYA survivors of pediatric cancers as well as their parental caregivers. Although these data coincide with other similar findings in the literature, there is a need to focus greater efforts on mitigating these high rates of depression among these AYA survivors. Specifically, particular attention should be paid to vulnerable populations who may not have access to mental health services. As this study found, AYA survivors without private insurance had greater odds of depression as compared to those without private insurance. Future efforts should incentivize making these services more accessible to survivors who are more at risk. By identifying those survivors and their families who may have less health insurance coverage, this may be an appropriate avenue for identifying a cohort of those at risk for depression in survivorship. Challenges to mitigating these disparities in mental health coverage remain for those with limited access to quality health coverage. It is important to acknowledge that mental health services are often hard to access, even for those who have greater health insurance coverage. Still, normalizing these discussions around mental health during treatment can help to increase the likelihood of survivors to continue this treatment trajectory as they transition to survivorship.

In addition, there is a greater need for increased funding to make these resources readily available to the growing community of AYA survivors. With an already dearth of mental health providers available, increased training for clinical teams to support these patients is greatly needed. Initiatives to help reach at-risk survivors, and increase services to rural and underserved areas, can help to increase these mental health services for these patients. Aside from increasing the access to these services, making these survivors aware of their risk for depression while they are still in active treatment is imperative. By normalizing these conversations with their oncology team and support system (including their caregivers), it can help to make these patients aware of their mental health needs as they transition towards survivorship. Since the stigma around mental health remains, normalizing the challenges that present from finishing cancer treatment and transitioning to survivorship must be addressed to help bridge these gaps. Educational campaigns as oncology teams prepare their patients to transition to survivorship may prove useful to help engage the patient and their caregivers about the long-term impacts of their cancer treatment on their mental health. Lastly, guidelines from the IGHG recommend surveillance of AYA survivors for a myriad of mental health outcomes.[29] The benefits to maintaining these screenings can help to track survivors that may no longer be actively in clinic as they transition into survivorship, and monitor these patients long after they have finished treatment but may still be at risk for depression.

Regarding future policy for caregivers of AYA survivors, increased focus should also attempt to maintain active dialogue with caregivers who face lasting impacts of their child's cancer diagnosis. This may include trying to mitigate some of the high levels of stress and burnout caregivers face during their time caring for their children during treatment. One option would be to expand access to respite care, which offers temporary relief services to primary caregivers. In offering this service, caregivers can take time away from the challenges of being a primary caregiver, allowing them to rest and relax. Expansion of programs that offer these services may help to mitigate long-term mental health impacts of the cancer experience on these caregivers.

Another potential policy recommendation includes increased caregiver education. Since the cancer experience is closely linked for both the AYA survivor and their caregiver, additional educational programs about managing caregiver's own mental health and well-being may prove useful as they navigate both on and off treatment for their survivors. Policies that increase these opportunities to engage with these programs may be helpful in normalizing these conversations for caregivers, thereby helping to increase the likelihood that they may seek mental health services in the event that they need them.

As survivors need greater access to mental health services, so too do their caregivers. The dearth of mental health services impacts both cohorts; therefore, policy makers should increase funding to offset the lack of clinicians available to address the mental health needs of caregivers. By increasing funding for initiatives that address mental health services, the high prevalence of depression in caregivers can hopefully be mitigated. Lastly, since being a primary caregiver for a pediatric cancer patient is incredibly stressful economically,[60-71] increasing financial support for these caregivers is vital to help offset some of the stress and burnout that they experience. Policies that can ease some of the expenses that caregivers will experience throughout the duration of their child's treatment and long after are necessary to do this. In addition, financial assistance programs that seek to support caregivers must be incentivized at health centers, and through governmental funding.

Ultimately, the findings of this analysis reflect a mixed consensus with previously recognized risk factors for depression in survivors. These aspects of cancer treatments must continue to be surveilled as they may help to identify those survivors most at risk for depression in survivorship. Future research should aim to investigate further the risk factors for depression in parental caregivers that this analysis was unable to discern. By increasing these conversations early on in the treatment process, the goal of increased mental health surveillance in survivorship for AYAs and their caregivers can potentially lead to decreased prevalence of depression in these cohorts that are at increased risk for it.

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. Jan 2023;73(1):17-48. doi:10.3322/caac.21763
2. Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol*. May 10 2009;27(14):2328-38. doi:10.1200/JCO.2008.21.1425
3. Armstrong GT, Chen Y, Yasui Y, et al. Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer. *N Engl J Med*. Mar 3 2016;374(9):833-42. doi:10.1056/NEJMoa1510795
4. Malvezzi M, Santucci C, Alicandro G, et al. Childhood cancer mortality trends in the Americas and Australasia: An update to 2017. *Cancer*. Sep 15 2021;127(18):3445-3456. doi:10.1002/cncr.33642
5. Bertuccio P, Alicandro G, Malvezzi M, et al. Childhood cancer mortality trends in Europe, 1990-2017, with focus on geographic differences. *Cancer Epidemiol*. Aug 2020;67:101768. doi:10.1016/j.canep.2020.101768
6. Smith L, Stiller CA, Aitken JF, et al. International variation in childhood cancer mortality rates from 2001 to 2015: Comparison of trends in the International Cancer Benchmarking Partnership countries. *Int J Cancer*. Jan 1 2022;150(1):28-37. doi:10.1002/ijc.33774
7. Ssenyonga N, Stiller C, Nakata K, et al. Worldwide trends in population-based survival for children, adolescents, and young adults diagnosed with leukaemia, by subtype, during 2000-14 (CONCORD-3): analysis of individual data from 258 cancer registries in 61 countries. *Lancet Child Adolesc Health*. Jun 2022;6(6):409-431. doi:10.1016/S2352-4642(22)00095-5
8. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer*. Jan 2014;14(1):61-70. doi:10.1038/nrc3634
9. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. Oct 12 2006;355(15):1572-82. doi:10.1056/NEJMsa060185
10. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA*. Jun 12 2013;309(22):2371-2381. doi:10.1001/jama.2013.6296
11. Landier W, Armenian S, Bhatia S. Late effects of childhood cancer and its treatment. *Pediatr Clin North Am*. Feb 2015;62(1):275-300. doi:10.1016/j.pcl.2014.09.017
12. Stotter BR, Chan C, Chanchlani R. Late Kidney Effects of Childhood Cancer and Cancer Therapies. *Adv Chronic Kidney Dis*. Sep 2021;28(5):490-501 e1. doi:10.1053/j.ackd.2021.09.001
13. Phillips SM, Padgett LS, Leisenring WM, et al. Survivors of childhood cancer in the United States: prevalence and burden of morbidity. *Cancer Epidemiol Biomarkers Prev*. Apr 2015;24(4):653-63. doi:10.1158/1055-9965.EPI-14-1418
14. Lund LW, Schmiegelow K, Rechnitzer C, Johansen C. A systematic review of studies on psychosocial late effects of childhood cancer: structures of society and methodological pitfalls may challenge the conclusions. *Pediatr Blood Cancer*. Apr 2011;56(4):532-43. doi:10.1002/pbc.22883
15. Friend AJ, Feltbower RG, Hughes EJ, Dye KP, Glaser AW. Mental health of long-term survivors of childhood and young adult cancer: A systematic review. *Int J Cancer*. Sep 15 2018;143(6):1279-1286. doi:10.1002/ijc.31337
16. Liu W, Yin Ting Cheung, Tara M. Brinkman, Pia Banerjee, Deokumar Srivastava, Vikki G Nolan, Hongmei Zhang, James G Gurney, Ching-Hon Pui, Leslie L. Robison, Melissa M. Hudson, Kevin R. Krull. Parent-Reported and Self-Perceived Behavioral and Psychiatric Symptoms in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia. *Blood*. 2016;128(22):3594. doi:https://doi.org/10.1182/blood.V128.22.3594.3594
17. Brinkman TM, Zhang N, Recklitis CJ, et al. Suicide ideation and associated mortality in adult survivors of childhood cancer. *Cancer*. Jan 15 2014;120(2):271-7. doi:10.1002/cncr.28385
18. Rebholz CE, Kuehni CE, Strippoli MP, et al. Alcohol consumption and binge drinking in young adult childhood cancer survivors. *Pediatr Blood Cancer*. Feb 2012;58(2):256-64. doi:10.1002/pbc.23289

19. Shah SS, Dellarole A, Peterson EC, et al. Long-term psychiatric outcomes in pediatric brain tumor survivors. *Childs Nerv Syst*. May 2015;31(5):653-63. doi:10.1007/s00381-015-2669-7
20. Landier W, Skinner R, Wallace WH, et al. Surveillance for Late Effects in Childhood Cancer Survivors. *J Clin Oncol*. Jul 20 2018;36(21):2216-2222. doi:10.1200/JCO.2017.77.0180
21. Hobbie WL, Li Y, Carlson C, et al. Late effects in survivors of high-risk neuroblastoma following stem cell transplant with and without total body irradiation. *Pediatr Blood Cancer*. Mar 2022;69(3):e29537. doi:10.1002/pbc.29537
22. Phelan R, Eissa H, Becktell K, et al. Upfront Therapies and Downstream Effects: Navigating Late Effects in Childhood Cancer Survivors in the Current Era. *Curr Oncol Rep*. Nov 25 2019;21(12):104. doi:10.1007/s11912-019-0861-8
23. Pasqual E, Schonfeld S, Morton LM, et al. Association Between Radioactive Iodine Treatment for Pediatric and Young Adulthood Differentiated Thyroid Cancer and Risk of Second Primary Malignancies. *J Clin Oncol*. May 1 2022;40(13):1439-1449. doi:10.1200/JCO.21.01841
24. Cohen-Cutler S, Olch A, Wong K, et al. Surveillance for radiation-related late effects in childhood cancer survivors: The impact of using volumetric dosimetry. *Cancer Med*. Feb 2021;10(3):905-913. doi:10.1002/cam4.3671
25. Mancilla TR, Iskra B, Aune GJ. Doxorubicin-Induced Cardiomyopathy in Children. *Compr Physiol*. Jun 12 2019;9(3):905-931. doi:10.1002/cphy.c180017
26. IGHG. International Guideline Harmonization Group for Late Effects of Childhood Cancer. IGHG. 2023. https://www.ighg.org
27. Mulder RL, Hudson MM, Bhatia S, et al. Updated Breast Cancer Surveillance Recommendations for Female Survivors of Childhood, Adolescent, and Young Adult Cancer From the International Guideline Harmonization Group. *J Clin Oncol*. Dec 10 2020;38(35):4194-4207. doi:10.1200/JCO.20.00562
28. Bowers DC, Verbruggen LC, Kremer LCM, et al. Surveillance for subsequent neoplasms of the CNS for childhood, adolescent, and young adult cancer survivors: a systematic review and recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol*. May 2021;22(5):e196-e206. doi:10.1016/S1470-2045(20)30688-4
29. Marchak JG, Christen S, Mulder RL, et al. Recommendations for the surveillance of mental health problems in childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol*. Apr 2022;23(4):e184-e196. doi:10.1016/S1470-2045(21)00750-6
30. Devine KA, Christen S, Mulder RL, et al. Recommendations for the surveillance of education and employment outcomes in survivors of childhood, adolescent, and young adult cancer: A report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Cancer*. Jul 1 2022;128(13):2405-2419. doi:10.1002/cncr.34215
31. Christen S, Roser K, Mulder RL, et al. Recommendations for the surveillance of cancer-related fatigue in childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *J Cancer Surviv*. Dec 2020;14(6):923-938. doi:10.1007/s11764-020-00904-9
32. van Dorp W, Mulder RL, Kremer LC, et al. Recommendations for Premature Ovarian Insufficiency Surveillance for Female Survivors of Childhood, Adolescent, and Young Adult Cancer: A Report From the International Late Effects of Childhood Cancer Guideline Harmonization Group in Collaboration With the PanCareSurFup Consortium. *J Clin Oncol*. Oct 1 2016;34(28):3440-50. doi:10.1200/JCO.2015.64.3288
33. Clemens E, van den Heuvel-Eibrink MM, Mulder RL, et al. Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium. *Lancet Oncol*. Jan 2019;20(1):e29-e41. doi:10.1016/S1470-2045(18)30858-1
34. Skinner R, Mulder RL, Kremer LC, et al. Recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects

of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Lancet Oncol*. Feb 2017;18(2):e75-e90. doi:10.1016/S1470-2045(17)30026-8

35. Armenian SH, Hudson MM, Mulder RL, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol*. Mar 2015;16(3):e123-36. doi:10.1016/S1470-2045(14)70409-7

36. Bardi E, Mulder RL, van Dalen EC, et al. Late hepatic toxicity surveillance for survivors of childhood, adolescent and young adult cancer: Recommendations from the international late effects of childhood cancer guideline harmonization group. *Cancer Treat Rev*. Nov 2021;100:102296. doi:10.1016/j.ctrv.2021.102296

37. van Iersel L, Mulder RL, Denzer C, et al. Hypothalamic-Pituitary and Other Endocrine Surveillance Among Childhood Cancer Survivors. *Endocr Rev*. Sep 26 2022;43(5):794-823. doi:10.1210/endrev/bnab040

38. Mulder RL, Font-Gonzalez A, Green DM, et al. Fertility preservation for male patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol*. Feb 2021;22(2):e57-e67. doi:10.1016/S1470-2045(20)30582-9

39. Mulder RL, Font-Gonzalez A, Hudson MM, et al. Fertility preservation for female patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol*. Feb 2021;22(2):e45-e56. doi:10.1016/S1470-2045(20)30594-5

40. van der Kooi ALF, Mulder RL, Hudson MM, et al. Counseling and surveillance of obstetrical risks for female childhood, adolescent, and young adult cancer survivors: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Am J Obstet Gynecol*. Jan 2021;224(1):3-15. doi:10.1016/j.ajog.2020.05.058

41. van Dalen EC, Mulder RL, Suh E, et al. Coronary artery disease surveillance among childhood, adolescent and young adult cancer survivors: A systematic review and recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Eur J Cancer*. Oct 2021;156:127-137. doi:10.1016/j.ejca.2021.06.021

42. Mulder RL, Font-Gonzalez A, van Dulmen-den Broeder E, et al. Communication and ethical considerations for fertility preservation for patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol*. Feb 2021;22(2):e68-e80. doi:10.1016/S1470-2045(20)30595-7

43. van Atteveld JE, Mulder RL, van den Heuvel-Eibrink MM, et al. Bone mineral density surveillance for childhood, adolescent, and young adult cancer survivors: evidence-based recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Diabetes Endocrinol*. Sep 2021;9(9):622-637. doi:10.1016/S2213-8587(21)00173-X

44. Clement SC, Kremer LCM, Verburg FA, et al. Balancing the benefits and harms of thyroid cancer surveillance in survivors of Childhood, adolescent and young adult cancer: Recommendations from the international Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Cancer Treat Rev*. Feb 2018;63:28-39. doi:10.1016/j.ctrv.2017.11.005

45. Long KA, Marsland AL. Family adjustment to childhood cancer: a systematic review. *Clin Child Fam Psychol Rev*. Mar 2011;14(1):57-88. doi:10.1007/s10567-010-0082-z

46. Brown RT, Madan-Swain A, Lambert R. Posttraumatic stress symptoms in adolescent survivors of childhood cancer and their mothers. *J Trauma Stress*. Aug 2003;16(4):309-18. doi:10.1023/A:1024465415620

47. Kronenberger WG, Carter BD, Edwards J, Morrow C, Stewart J, Sender L. Psychological Adjustment of Mothers of Children Undergoing Bone Marrow Transplantation: The Role of Stress,

Coping, and Family Factors. *Children's Health Care*. 1998/04/01 1998;27(2):77-95. doi:10.1207/s15326888chc2702_1
48. Kazak AE, Barakat LP, Meeske K, et al. Posttraumatic stress, family functioning, and social support in survivors of childhood leukemia and their mothers and fathers. *J Consult Clin Psychol*. Feb 1997;65(1):120-9. doi:10.1037//0022-006x.65.1.120
49. Foley B, Barakat LP, Herman-Liu A, Radcliffe J, Molloy P. The Impact of Childhood Hypothalamic/Chiasmatic Brain Tumors on Child Adjustment and Family Functioning. *Children's Health Care*. 2000/09/01 2000;29(3):209-222. doi:10.1207/S15326888CHC2903_5
50. Bjork M, Wiebe T, Hallstrom I. Striving to survive: families' lived experiences when a child is diagnosed with cancer. *J Pediatr Oncol Nurs*. Sep-Oct 2005;22(5):265-75. doi:10.1177/1043454205279303
51. Brody AC, Simmons LA. Family resiliency during childhood cancer: the father's perspective. *J Pediatr Oncol Nurs*. May-Jun 2007;24(3):152-65. doi:10.1177/1043454206298844
52. Chesler MA, Parry C. Gender roles and/or styles in crisis: an integrative analysis of the experiences of fathers of children with cancer. *Qual Health Res*. May 2001;11(3):363-84. doi:10.1177/104973230101100307
53. Clarke-Steffen L. Reconstructing reality: family strategies for managing childhood cancer. *J Pediatr Nurs*. Oct 1997;12(5):278-87. doi:10.1016/S0882-5963(97)80045-0
54. Enskar K, Carlsson M, Golsater M, Hamrin E, Kreuger A. Parental reports of changes and challenges that result from parenting a child with cancer. *J Pediatr Oncol Nurs*. Jul 1997;14(3):156-63. doi:10.1016/s1043-4542(97)90051-5
55. Fletcher PC, Clarke J. When Your Child Has Cancer. *Journal of Psychosocial Oncology*. 2003/12/31 2003;21(3):81-99. doi:10.1300/J077v21n03_05
56. De Graves S, Aranda S. Living with hope and fear--the uncertainty of childhood cancer after relapse. *Cancer Nurs*. Jul-Aug 2008;31(4):292-301. doi:10.1097/01.NCC.0000305745.41582.73
57. Freeman K, O'Dell C, Meola C. Issues in families of children with brain tumors. *Oncol Nurs Forum*. Jun 2000;27(5):843-8.
58. Harrington AD, Kimball TG, Bean RA. Families and childhood cancer: an exploration of the observations of a pediatric oncology treatment team. *Fam Syst Health*. Mar 2009;27(1):16-27. doi:10.1037/a0014909
59. Jones JB, Neil-Urban S. Father to father: focus groups of fathers of children with cancer. *Soc Work Health Care*. 2003;37(1):41-61. doi:10.1300/J010v37n01_03
60. Roser K, Erdmann F, Michel G, Winther JF, Mader L. The impact of childhood cancer on parents' socio-economic situation-A systematic review. *Psychooncology*. Jun 2019;28(6):1207-1226. doi:10.1002/pon.5088
61. Lahteenmaki PM, Sjoblom J, Korhonen T, Salmi TT. The life situation of parents over the first year after their child's cancer diagnosis. *Acta Paediatr*. Dec 2004;93(12):1654-60.
62. Syse A, Larsen IK, Tretli S. Does cancer in a child affect parents' employment and earnings? A population-based study. *Cancer Epidemiol*. Jun 2011;35(3):298-305. doi:10.1016/j.canep.2010.08.002
63. Hoven E, von Essen L, Norberg AL. A longitudinal assessment of work situation, sick leave, and household income of mothers and fathers of children with cancer in Sweden. *Acta Oncol*. Aug 2013;52(6):1076-85. doi:10.3109/0284186X.2012.760846
64. Lindahl Norberg A, Montgomery SM, Bottai M, Heyman M, Hoven EI. Short-term and long-term effects of childhood cancer on income from employment and employment status: A national cohort study in Sweden. *Cancer*. Apr 1 2017;123(7):1238-1248. doi:10.1002/cncr.30436
65. Wikman A, Hoven E, Cernvall M, Ljungman G, Ljungman L, von Essen L. Parents of children diagnosed with cancer: work situation and sick leave, a five-year post end-of-treatment or a child's death follow-up study. *Acta Oncol*. Sep-Oct 2016;55(9-10):1152-1157. doi:10.3109/0284186X.2016.1167956
66. Mader L, Rueegg CS, Vetsch J, et al. Employment Situation of Parents of Long-Term Childhood Cancer Survivors. *PLoS One*. 2016;11(3):e0151966. doi:10.1371/journal.pone.0151966

67. Eiser C, Upton P. Costs of caring for a child with cancer: a questionnaire survey. *Child Care Health Dev*. Jul 2007;33(4):455-9. doi:10.1111/j.1365-2214.2006.00710.x

68. Tsimicalis A, Stevens B, Ungar WJ, et al. A prospective study to determine the costs incurred by families of children newly diagnosed with cancer in Ontario. *Psychooncology*. Oct 2012;21(10):1113-23. doi:10.1002/pon.2009

69. Limburg H, Shaw AK, McBride ML. Impact of childhood cancer on parental employment and sources of income: a Canadian pilot study. *Pediatr Blood Cancer*. Jul 2008;51(1):93-8. doi:10.1002/pbc.21448

70. Bona K, Dussel V, Orellana L, et al. Economic impact of advanced pediatric cancer on families. *J Pain Symptom Manage*. Mar 2014;47(3):594-603. doi:10.1016/j.jpainsymman.2013.04.003

71. Hiyoshi A, Montgomery S, Bottai M, Hoven EI. Trajectories of income and social benefits for mothers and fathers of children with cancer: A national cohort study in Sweden. *Cancer*. Apr 1 2018;124(7):1492-1500. doi:10.1002/cncr.31123

72. APA. Depressive Disorders. *Diagnostic and Statistical Manual of Mental Disorders*. 2022.

73. Friedrich MJ. Depression Is the Leading Cause of Disability Around the World. *JAMA*. Apr 18 2017;317(15):1517. doi:10.1001/jama.2017.3826

74. HHS Publication No. PEP21-07-01-003, NSDUH Series H-56 Key substance use and mental health indicators in the United States: Results from the 2020 National Survey on Drug Use and Health (Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration) (2021).

75. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry*. Apr 1 2018;75(4):336-346. doi:10.1001/jamapsychiatry.2017.4602

76. Mojtabai R, Olfson M, Han B. National Trends in the Prevalence and Treatment of Depression in Adolescents and Young Adults. *Pediatrics*. Dec 2016;138(6)doi:10.1542/peds.2016-1878

77. Kunin-Batson AS, Lu X, Balsamo L, et al. Prevalence and predictors of anxiety and depression after completion of chemotherapy for childhood acute lymphoblastic leukemia: A prospective longitudinal study. *Cancer*. May 15 2016;122(10):1608-17. doi:10.1002/cncr.29946

78. Perez GK, Kirchhoff AC, Recklitis C, et al. Mental health insurance access and utilization among childhood cancer survivors: a report from the childhood cancer survivor study. *J Cancer Surviv*. Aug 2018;12(4):528-536. doi:10.1007/s11764-018-0691-y

79. Robison LL, Mertens AC, Boice JD, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Med Pediatr Oncol*. Apr 2002;38(4):229-39. doi:10.1002/mpo.1316

80. 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*. May 10 2009;27(14):2308-18. doi:10.1200/JCO.2009.22.3339

81. Brinkman TM, Lown EA, Li C, et al. Alcohol consumption behaviors and neurocognitive dysfunction and emotional distress in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Addiction*. Feb 2019;114(2):226-235. doi:10.1111/add.14439

82. Krull KR, Huang S, Gurney JG, et al. Adolescent behavior and adult health status in childhood cancer survivors. *J Cancer Surviv*. Sep 2010;4(3):210-7. doi:10.1007/s11764-010-0123-0

83. Brinkman TM, Zhu L, Zeltzer LK, et al. Longitudinal patterns of psychological distress in adult survivors of childhood cancer. *Br J Cancer*. Sep 3 2013;109(5):1373-81. doi:10.1038/bjc.2013.428

84. Vuotto SC, Krull KR, Li C, et al. Impact of chronic disease on emotional distress in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Cancer*. Feb 1 2017;123(3):521-528. doi:10.1002/cncr.30348

85. Huang IC, Brinkman TM, Armstrong GT, Leisenring W, Robison LL, Krull KR. Emotional distress impacts quality of life evaluation: a report from the Childhood Cancer Survivor Study. *J Cancer Surviv*. Jun 2017;11(3):309-319. doi:10.1007/s11764-016-0589-5

86. Brinkman TM, Li C, Vannatta K, et al. Behavioral, Social, and Emotional Symptom Comorbidities and Profiles in Adolescent Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol*. Oct 1 2016;34(28):3417-25. doi:10.1200/JCO.2016.66.4789
87. Prasad PK, Hardy KK, Zhang N, et al. Psychosocial and Neurocognitive Outcomes in Adult Survivors of Adolescent and Early Young Adult Cancer: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol*. Aug 10 2015;33(23):2545-52. doi:10.1200/JCO.2014.57.7528
88. Dixon SB, Li N, Yasui Y, et al. Racial and ethnic disparities in neurocognitive, emotional, and quality-of-life outcomes in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Cancer*. Oct 15 2019;125(20):3666-3677. doi:10.1002/cncr.32370
89. Stefanski KJ, Anixt JS, Goodman P, et al. Long-Term Neurocognitive and Psychosocial Outcomes After Acute Myeloid Leukemia: A Childhood Cancer Survivor Study Report. *J Natl Cancer Inst*. Apr 6 2021;113(4):481-495. doi:10.1093/jnci/djaa102
90. Tonorezos ES, Ford JS, Wang L, et al. Impact of exercise on psychological burden in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Cancer*. Sep 1 2019;125(17):3059-3067. doi:10.1002/cncr.32173
91. Kirchhoff AC, Krull KR, Ness KK, et al. Physical, mental, and neurocognitive status and employment outcomes in the childhood cancer survivor study cohort. *Cancer Epidemiol Biomarkers Prev*. Sep 2011;20(9):1838-49. doi:10.1158/1055-9965.EPI-11-0239
92. Weinstein AG, Henrich CC, Armstrong GT, et al. Roles of positive psychological outcomes in future health perception and mental health problems: A report from the Childhood Cancer Survivor Study. *Psychooncology*. Dec 2018;27(12):2754-2760. doi:10.1002/pon.4881
93. Kadan-Lottick NS, Zeltzer LK, Liu Q, et al. Neurocognitive functioning in adult survivors of childhood non-central nervous system cancers. *J Natl Cancer Inst*. Jun 16 2010;102(12):881-93. doi:10.1093/jnci/djq156
94. Papini C, Fayad AA, Wang M, et al. Emotional, behavioral, and physical health consequences of loneliness in young adult survivors of childhood cancer: Results from the Childhood Cancer Survivor Study. *Cancer*. Apr 1 2023;129(7):1117-1128. doi:10.1002/cncr.34633
95. Franke GH, Ankerhold A, Haase M, et al. [The usefulness of the Brief Symptom Inventory 18 (BSI-18) in psychotherapeutic patients]. *Psychother Psychosom Med Psychol*. Feb 2011;61(2):82-6. Der Einsatz des Brief Symptom Inventory 18 (BSI-18) bei Psychotherapiepatienten. doi:10.1055/s-0030-1270518
96. Schultz KA, Ness KK, Whitton J, et al. Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol*. Aug 20 2007;25(24):3649-56. doi:10.1200/JCO.2006.09.2486
97. Zill N, Peterson JL. Behavior problems index. *Washington, DC: Child Trends*. 1986;
98. Carpentieri SC, Meyer EA, Delaney BL, et al. Psychosocial and behavioral functioning among pediatric brain tumor survivors. *J Neurooncol*. Jul 2003;63(3):279-87. doi:10.1023/a:1024203323830
99. Foreman NK, Faestel PM, Pearson J, et al. Health status in 52 long-term survivors of pediatric brain tumors. *J Neurooncol*. Jan 1999;41(1):47-53. doi:10.1023/a:1006145724500
100. Turkel SB, Tishler D, Tavare CJ. Late onset psychosis in survivors of pediatric central nervous system malignancies. *J Neuropsychiatry Clin Neurosci*. Summer 2007;19(3):293-7. doi:10.1176/jnp.2007.19.3.293
101. Sands SA, Zhou T, O'Neil SH, et al. Long-term follow-up of children treated for high-grade gliomas: children's oncology group L991 final study report. *J Clin Oncol*. Mar 20 2012;30(9):943-9. doi:10.1200/JCO.2011.35.7533
102. Turner CD, Chordas CA, Liptak CC, et al. Medical, psychological, cognitive and educational late-effects in pediatric low-grade glioma survivors treated with surgery only. *Pediatr Blood Cancer*. Sep 2009;53(3):417-23. doi:10.1002/pbc.22081
103. van der Geest IM, van Dorp W, Hop WC, et al. Emotional distress in 652 Dutch very long-term survivors of childhood cancer, using the hospital anxiety and depression scale (HADS). *J Pediatr Hematol Oncol*. Oct 2013;35(7):525-9. doi:10.1097/MPH.0b013e31829f2799

104. Zebrack BJ, Gurney JG, Oeffinger K, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the childhood cancer survivor study. *J Clin Oncol*. Mar 15 2004;22(6):999-1006. doi:10.1200/JCO.2004.06.148

105. Daszkiewicz P, Maryniak A, Roszkowski M, Barszcz S. Long-term functional outcome of surgical treatment of juvenile pilocytic astrocytoma of the cerebellum in children. *Childs Nerv Syst*. Jul 2009;25(7):855-60. doi:10.1007/s00381-009-0855-1

106. Zebrack BJ, Zevon MA, Turk N, et al. Psychological distress in long-term survivors of solid tumors diagnosed in childhood: a report from the childhood cancer survivor study. *Pediatr Blood Cancer*. Jul 2007;49(1):47-51. doi:10.1002/pbc.20914

107. Ander M, Gronqvist H, Cernvall M, et al. Development of health-related quality of life and symptoms of anxiety and depression among persons diagnosed with cancer during adolescence: a 10-year follow-up study. *Psychooncology*. May 2016;25(5):582-9. doi:10.1002/pon.3965

108. Lof CM, Winiarski J, Giesecke A, Ljungman P, Forinder U. Health-related quality of life in adult survivors after paediatric allo-SCT. *Bone Marrow Transplant*. Mar 2009;43(6):461-8. doi:10.1038/bmt.2008.338

109. Ahomaki R, Gunn ME, Madanat-Harjuoja LM, Matomaki J, Malila N, Lahteenmaki PM. Late psychiatric morbidity in survivors of cancer at a young age: a nationwide registry-based study. *Int J Cancer*. Jul 1 2015;137(1):183-92. doi:10.1002/ijc.29371

110. Lehmann V, Gronqvist H, Engvall G, et al. Negative and positive consequences of adolescent cancer 10 years after diagnosis: an interview-based longitudinal study in Sweden. *Psychooncology*. Nov 2014;23(11):1229-35. doi:10.1002/pon.3549

111. Schapiro M, Hayashi, R. J. , Liu, W. , Srivastava, D. K. , Jeffe, D. , Perkins, S. M. , Armstrong, G. T. , Robison, L. L. , Stovall, M. , Leisenring, W. M. & Krull, K. R. Neurocognitive, emotional, and quality of life outcomes in long-term survivors of rhabdomyosarcoma: A report from the Childhood Cancer Survivor Study (CCSS). *Journal of Clinical Oncology*. 2015;33(15)doi:10.1200/jco.2015.33.15_suppl.10072

112. Seitz DC, Besier T, Debatin KM, et al. Posttraumatic stress, depression and anxiety among adult long-term survivors of cancer in adolescence. *Eur J Cancer*. Jun 2010;46(9):1596-606. doi:10.1016/j.ejca.2010.03.001

113. Sanders JE, Hoffmeister PA, Storer BE, Appelbaum FR, Storb RF, Syrjala KL. The quality of life of adult survivors of childhood hematopoietic cell transplant. *Bone Marrow Transplant*. Apr 2010;45(4):746-54. doi:10.1038/bmt.2009.224

114. Deyell RJ, Lorenzi M, Ma S, et al. Antidepressant use among survivors of childhood, adolescent and young adult cancer: a report of the Childhood, Adolescent and Young Adult Cancer Survivor (CAYACS) Research Program. *Pediatr Blood Cancer*. May 2013;60(5):816-22. doi:10.1002/pbc.24446

115. Poretti A, Grotzer MA, Ribi K, Schonle E, Boltshauser E. Outcome of craniopharyngioma in children: long-term complications and quality of life. *Dev Med Child Neurol*. Apr 2004;46(4):220-9. doi:10.1017/s0012162204000374

116. Ashford JM, Netson KL, Clark KN, et al. Adaptive functioning of childhood brain tumor survivors following conformal radiation therapy. *J Neurooncol*. May 2014;118(1):193-9. doi:10.1007/s11060-014-1420-7

117. Pepin AJ, Lippe S, Krajinovic M, et al. How to interpret high levels of distress when using the Distress Thermometer in the long-term follow-up clinic? A study with Acute Lymphoblastic Leukemia survivors. *Pediatr Hematol Oncol*. Apr 2017;34(3):133-137. doi:10.1080/08880018.2017.1338805

118. Anestin AS, Lippe S, Robaey P, et al. Psychological risk in long-term survivors of childhood acute lymphoblastic leukemia and its association with functional health status: A PETALE cohort study. *Pediatr Blood Cancer*. Nov 2018;65(11):e27356. doi:10.1002/pbc.27356

119. Dieluweit U, Seitz DC, Besier T, et al. Utilization of psychosocial care and oncological follow-up assessments among German long-term survivors of cancer with onset during adolescence. *Klin Padiatr*. May 2011;223(3):152-8. doi:10.1055/s-0031-1271779

120. Gianinazzi ME, Rueegg CS, Wengenroth L, et al. Adolescent survivors of childhood cancer: are they vulnerable for psychological distress? *Psychooncology*. Sep 2013;22(9):2051-8. doi:10.1002/pon.3249
121. Michel G, Rebholz CE, von der Weid NX, Bergstraesser E, Kuehni CE. Psychological distress in adult survivors of childhood cancer: the Swiss Childhood Cancer Survivor study. *J Clin Oncol*. Apr 1 2010;28(10):1740-8. doi:10.1200/JCO.2009.23.4534
122. Burghardt J, Klein E, Brahler E, et al. Prevalence of mental distress among adult survivors of childhood cancer in Germany-Compared to the general population. *Cancer Med*. Apr 2019;8(4):1865-1874. doi:10.1002/cam4.1936
123. Zheng DJ, Krull KR, Chen Y, et al. Long-term psychological and educational outcomes for survivors of neuroblastoma: A report from the Childhood Cancer Survivor Study. *Cancer*. Aug 1 2018;124(15):3220-3230. doi:10.1002/cncr.31379
124. Recklitis CJ, Parsons SK, Shih MC, Mertens A, Robison LL, Zeltzer L. Factor structure of the brief symptom inventory--18 in adult survivors of childhood cancer: results from the childhood cancer survivor study. *Psychol Assess*. Mar 2006;18(1):22-32. doi:10.1037/1040-3590.18.1.22
125. Meeske KA, Sherman-Bien S, Hamilton AS, et al. Mental health disparities between Hispanic and non-Hispanic parents of childhood cancer survivors. *Pediatr Blood Cancer*. Sep 2013;60(9):1470-7. doi:10.1002/pbc.24527
126. Manikowski A, Williamson Lewis R, Bennett T, et al. Implementation of Electronic Psychosocial Screening Among Caregivers in Pediatric Oncology. *JCO Oncol Pract*. Jul 2022;18(7):e1198-e1208. doi:10.1200/OP.21.00836
127. Quast LF, Williamson Lewis R, Lee JL, Blount RL, Gilleland Marchak J. Psychosocial Functioning Among Caregivers of Childhood Cancer Survivors Following Treatment Completion. *J Pediatr Psychol*. Oct 18 2021;46(10):1238-1248. doi:10.1093/jpepsy/jsab061
128. Hardy KK, Bonner MJ, Masi R, Hutchinson KC, Willard VW, Rosoff PM. Psychosocial functioning in parents of adult survivors of childhood cancer. *J Pediatr Hematol Oncol*. Feb 2008;30(2):153-9. doi:10.1097/MPH.0b013e31815814d9
129. Bates CR, Fairclough D, Noll RB, et al. Psychosocial functioning of caregivers of pediatric brain tumor survivors. *Pediatr Blood Cancer*. Apr 2022;69(4):e29565. doi:10.1002/pbc.29565
130. Cho IY, Chung NG, Baek HJ, et al. Health behaviors of caregivers of childhood cancer survivors: a cross-sectional study. *BMC Cancer*. Apr 7 2020;20(1):296. doi:10.1186/s12885-020-06765-w
131. Christen S, Mader L, Baenziger J, et al. "I wish someone had once asked me how I'm doing": Disadvantages and support needs faced by parents of long-term childhood cancer survivors. *Pediatr Blood Cancer*. Aug 2019;66(8):e27767. doi:10.1002/pbc.27767
132. Wikman A, Mattsson E, von Essen L, Hoven E. Prevalence and predictors of symptoms of anxiety and depression, and comorbid symptoms of distress in parents of childhood cancer survivors and bereaved parents five years after end of treatment or a child's death. *Acta Oncol*. Jul 2018;57(7):950-957. doi:10.1080/0284186X.2018.1445286
133. Peikert ML, Inhestern L, Krauth KA, et al. Fear of progression in parents of childhood cancer survivors: prevalence and associated factors. *J Cancer Surviv*. Aug 2022;16(4):823-833. doi:10.1007/s11764-021-01076-w
134. Gutierrez-Colina AM, Lee JL, VanDellen M, et al. Family Functioning and Depressive Symptoms in Adolescent and Young Adult Cancer Survivors and Their Families: A Dyadic Analytic Approach. *J Pediatr Psychol*. Jan 1 2017;42(1):19-27. doi:10.1093/jpepsy/jsw041
135. Ochoa CY, Cho J, Miller KA, et al. Hispanic/Latinos and non-Hispanic whites' childhood cancer survivors and parents: a dyadic analysis of coping resources and mental health. *J Cancer Surviv*. Feb 28 2023;doi:10.1007/s11764-023-01339-8
136. Ozono S, Saeki T, Mantani T, et al. Psychological distress related to patterns of family functioning among Japanese childhood cancer survivors and their parents. *Psychooncology*. May 2010;19(5):545-52. doi:10.1002/pon.1606

137. Lemetayer F, Florquin M, Chastagner P, Lanfranchi JB. Life engagement and anxiety-depressive symptoms in adolescents and young adults with or without a cancer history and their mothers: A dyadic analytic approach. *Eur J Cancer Care (Engl)*. Nov 2022;31(6):e13745. doi:10.1111/ecc.13745

138. Karimi M, Cox AD, White SV, Karlson CW. Fatigue, Physical and Functional Mobility, and Obesity in Pediatric Cancer Survivors. *Cancer Nurs*. Jul/Aug 2020;43(4):E239-E245. doi:10.1097/NCC.0000000000000712

139. Ramsey LH, Graves PE, Howard Sharp KM, Seals SR, Collier AB, Karlson CW. Impact of Race and Socioeconomic Status on Psychologic Outcomes in Childhood Cancer Patients and Caregivers. *J Pediatr Hematol Oncol*. Aug 2019;41(6):433-437. doi:10.1097/MPH.0000000000001405

140. McCarthy MC, McNeil R, Drew S, et al. Psychological Distress and Posttraumatic Stress Symptoms in Adolescents and Young Adults with Cancer and Their Parents. *J Adolesc Young Adult Oncol*. Dec 2016;5(4):322-329. doi:10.1089/jayao.2016.0015

141. Litzelman K, Yabroff KR. How are spousal depressed mood, distress, and quality of life associated with risk of depressed mood in cancer survivors? Longitudinal findings from a national sample. *Cancer Epidemiol Biomarkers Prev*. Jun 2015;24(6):969-77. doi:10.1158/1055-9965.EPI-14-1420

142. Pilkonis PA, Choi SW, Reise SP, et al. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger. *Assessment*. Sep 2011;18(3):263-83. doi:10.1177/1073191111411667

143. Pilkonis PA, Yu L, Dodds NE, Johnston KL, Maihoefer CC, Lawrence SM. Validation of the depression item bank from the Patient-Reported Outcomes Measurement Information System (PROMIS) in a three-month observational study. *J Psychiatr Res*. Sep 2014;56:112-9. doi:10.1016/j.jpsychires.2014.05.010

144. Kroenke K, Stump TE, Chen CX, et al. Responsiveness of PROMIS and Patient Health Questionnaire (PHQ) Depression Scales in three clinical trials. *Health Qual Life Outcomes*. Feb 4 2021;19(1):41. doi:10.1186/s12955-021-01674-3

145. Schalet BD, Pilkonis PA, Yu L, et al. Clinical validity of PROMIS Depression, Anxiety, and Anger across diverse clinical samples. *J Clin Epidemiol*. May 2016;73:119-27. doi:10.1016/j.jclinepi.2015.08.036

146. APA. PROMIS- Depression Instrument. Health Measures. February 4, 2023, 2023. 2023. https://staging.healthmeasures.net/images/PROMIS/manuals/PROMIS_Depression_Scoring_Manual.pdf

147. Kazak AE, Hocking MC, Ittenbach RF, et al. A revision of the intensity of treatment rating scale: classifying the intensity of pediatric cancer treatment. *Pediatr Blood Cancer*. Jul 15 2012;59(1):96-9. doi:10.1002/pbc.23320

148. Werba BE, Hobbie W, Kazak AE, Ittenbach RF, Reilly AF, Meadows AT. Classifying the intensity of pediatric cancer treatment protocols: the intensity of treatment rating scale 2.0 (ITR-2). *Pediatr Blood Cancer*. Jun 15 2007;48(7):673-7. doi:10.1002/pbc.21184

149. COG. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers Version 5.0. October 2018. www.survivorshipguidelines.org

150. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. *Qual Life Res*. Sep 2009;18(7):873-80. doi:10.1007/s11136-009-9496-9

151. Singh S, Roy D, Sinha K, Parveen S, Sharma G, Joshi G. Impact of COVID-19 and lockdown on mental health of children and adolescents: A narrative review with recommendations. *Psychiatry Res*. Nov 2020;293:113429. doi:10.1016/j.psychres.2020.113429

152. Lee J, Solomon M, Stead T, Kwon B, Ganti L. Impact of COVID-19 on the mental health of US college students. *BMC Psychol*. Jun 8 2021;9(1):95. doi:10.1186/s40359-021-00598-3

153. Kola L, Kohrt BA, Hanlon C, et al. COVID-19 mental health impact and responses in low-income and middle-income countries: reimagining global mental health. *Lancet Psychiatry*. Jun 2021;8(6):535-550. doi:10.1016/S2215-0366(21)00025-0

154. Wang X, Hegde S, Son C, Keller B, Smith A, Sasangohar F. Investigating Mental Health of US College Students During the COVID-19 Pandemic: Cross-Sectional Survey Study. *J Med Internet Res*. Sep 17 2020;22(9):e22817. doi:10.2196/22817

155. Walker ER, Cummings JR, Hockenberry JM, Druss BG. Insurance status, use of mental health services, and unmet need for mental health care in the United States. *Psychiatr Serv*. Jun 2015;66(6):578-84. doi:10.1176/appi.ps.201400248

156. Derigne L, Porterfield S, Metz S. The influence of health insurance on parent's reports of children's unmet mental health needs. *Matern Child Health J*. Mar 2009;13(2):176-86. doi:10.1007/s10995-008-0346-0

157. Chen J, Vargas-Bustamante A. Estimating the effects of immigration status on mental health care utilizations in the United States. *J Immigr Minor Health*. Aug 2011;13(4):671-80. doi:10.1007/s10903-011-9445-x