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Functional Outcomes and Social Attainment in Asian/Pacific Islander Childhood Cancer Survivors in the United States: A Report from the Childhood Cancer Survivor Study

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Abstract

Background: Given the relatively small population of Asians or Pacific Islanders (API) in the United States, studies describing long-term outcomes in API survivors of childhood cancer are limited. This study compared functional outcomes between API *versus* non-Hispanic White (NHW) survivors.

Methods: This study included 203 API five-year survivors (age at follow-up: 29.2 [SD=6.3] years) and 12,186 NHW survivors (age at follow-up 31.5 [SD=7.3] years) from the Childhood Cancer Survivor Study. Self-reported functional outcomes of neurocognitive function, emotional distress, quality of life, and social attainment were compared between the two groups using multivariable regression, adjusted for sex, age at diagnosis and evaluation, cancer diagnosis, and neurotoxic treatment.

Results: No statistically significant race/ethnicity-based differences were identified in neurocognitive and emotional measures. API survivors reported, on average, less bodily pain than NHW survivors (mean 54.11 [SD=8.98] vs. 51.32 [SD=10.12]; $P<.001$). NHW survivors were less likely to have attained at least a college degree than API survivors (odds ratio[OR]=0.50; 95% confidence interval[CI]=0.34, 0.73). API survivors were more likely than NHW survivors to be never-married (OR=2.83, 95% CI=1.93, 4.13) and to live dependently (OR=3.10; 95% CI=2.02, 4.74). Older age (>45 years), brain tumor diagnosis, and higher cranial radiation dose were associated with poorer functional outcomes in API survivors (all, $P's<0.05$).

Conclusion: We observed differences in social attainment between API and NHW survivors, though statistically significant differences in neurocognitive and emotional outcomes were not identified.

Impact: Future studies should evaluate whether racial/ethnic differences in environmental and sociocultural factors may have differential effects on health and functional outcomes.

Keywords

Childhood cancer; survivors; functional; emotional; neurocognitive; social attainment; Asian; Pacific Islander; ethnicity; minority

Introduction

Contemporary treatment strategies have contributed to a decline in mortality among survivors of childhood cancer.[1] However, survivorship comes at a cost of being at elevated risk for a variety of chronic health conditions associated with cancer diagnosis and/or treatment, compromised health status that can last a lifetime. Long-term survivors of childhood cancer are also at risk of developing neurocognitive deficits and psychological distress.[2–7] Reports from the Childhood Cancer Survivor Study (CCSS) have stated that up to a third of survivors report problems with task efficiency, memory, organization, or emotional regulation.[6,8–10] Survivors are also more likely than their siblings to report symptoms of anxiety, depression, somatization, and suicidal ideation.[2,5,10–12] Consequently, neurocognitive deficits and psychosocial distress can have negative effects on survivors' health-related qualify of life (HRQoL), social attainment, and functional independence.[8,13–15] The risk factors for poor functional outcomes in survivors of

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childhood cancer are well documented in the literature, and include central nervous system (CNS) cancers and CNS-directed therapies, such as cranial radiation (CRT), intrathecal chemotherapy, and high-dose systemic methotrexate.[16,17] As survivors age, frailty and chronic health conditions such as cardiopulmonary and endocrine complications can also lead to worse functional outcomes.[7,12,17–20]

In addition to clinical and treatment predictors, differences by race and ethnicity in these outcomes have become the focus of emerging research. One report by the CCSS showed that compared with non-Hispanic White (NHW) survivors, non-Hispanic Black (NHB) and Hispanic survivors are three times more likely to report moderate-to-severe endocrine complications even after adjusting for socioeconomic status and obesity.[21] Another recent CCSS report did not identify differences in neurocognitive function between Hispanic, NHB, and NHW survivors, but the minority survivors reported poorer HRQoL outcomes than NHW survivors, and this disparity became more evident as the survivors aged.[22] These studies suggest that the burden of morbidity borne by childhood cancer survivors differs by race and ethnicity. However, it is important to highlight that neither of these previous reports examine functional outcomes specifically in survivors of Asian or Pacific Islander (API) descent, members of the most populous group in the world.

The API population in the United States is a unique and heterogeneous group, due to broad historical immigration patterns. Differences in cancer incidence and survival patterns have been reported between API and other racial/ethnic groups.[23,24] Unfortunately, given the relatively small population of API individuals in the United States, studies describing the health and functional outcomes in childhood cancer survivors in this population are limited. One recently published study revealed that compared with NHW children and adolescents, non-Hispanic API patients exhibited a higher risk of death from high- and low-amenability cancers.[25] Genetic variations may account for the observed variations in treatment outcomes and risk profiles for exposure-related late effects.[26] External factors such as the socioeconomic status, cultural values, and family functioning may also contribute to differences in mental health and HRQoL outcomes between cancer patients of NHW and API descents.[23,26] These observations highlight the need to comprehensively assess the psychosocial and functional outcomes of API survivors of childhood cancer in the United States.

The objectives of this study were to (1) compare neurocognitive function, emotional distress, HRQoL, and social attainment outcomes between API survivors of childhood cancer and sibling controls, (2) compare differences in outcomes between API and NHW survivors, and (3) identify the factors associated with these outcomes in API survivors.

Materials and Methods

Participants

The CCSS is a multi-institutional retrospectively-constructed cohort with prospective follow-up of 5-year survivors of childhood cancer. It includes survivors diagnosed with cancer between 1970 and 1999 at an age younger than 21 years.[27,28] Multiple cancer diagnoses were included. Institutional review boards at the 31 participating institutions

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approved the CCSS study protocol, and all participants provided written informed consent in accordance with the Declaration of Helsinki. At cohort entry, survivors identified a living sibling nearest to them in age. A random sample of siblings were contacted to participate, and they served as the comparison population for functional outcomes of this study.[27,28] With the exception of cancer-specific topics, information collected from the sibling cohort is identical to that obtained on the survivor population.

All participants completed a baseline questionnaire assessing their demographic factors. Information on socioeconomic factors and health-related outcomes were obtained during follow-up assessment in 2003 or 2015. Race/ethnicity information was obtained using self-reported race categories of White, Black, American Indian or Alaska Native (AIAN), API, or Other (with the option to write in their race). Hispanic ethnicity was reported through a separate binary (yes/no) question. For this study, 14,498 eligible survivors and 3,282 siblings completed both the baseline and follow-up questionnaires on functional outcomes in 2003, 2007 or 2015. We excluded participants in the AIAN (n=82), Black (n=654), Hispanic (n = 587), and Other racial categories (n=786), leaving two mutually exclusive race/ethnicity populations, NHW and API (Supplementary Figure 1).

Outcomes

Neurocognitive outcomes were measured using the CCSS-Neurocognitive Questionnaire (CCSS-NCQ), a 25-item instrument that has previously been validated in CCSS survivors and siblings.[29] It consists of four domains: task efficiency, emotional regulation, organization, and memory. Raw scores were converted to *T*-scores with reference to sibling norms (mean=50, standard deviation [SD]=10 in siblings), with higher scores indicating more neurocognitive problems. Consistent with other CCSS publications, neurocognitive impairment in this study was defined as a T-score ≥90th percentile of the sibling T-score distribution for each domain.

Emotional distress was measured using the Brief-Symptom Inventory-18 (BSI-18), which includes subscales for anxiety, depression, and somatization.[30] Sex-specific *T*-scores were calculated based on standardized normative values.[30] A higher score is indicative of a higher level of emotional distress. Participants with T-scores ≥90th percentile were classified as presenting with clinically significant levels of emotional distress.

The HRQoL was measured using the 36-Item Short Form Health Survey (SF-36) from the Medical Outcomes Survey, which includes eight domains: general health, physical role, physical function, bodily pain, vitality, mental health, social function, and emotional role.[31] Scores for each domain were converted into *T*-scores based on age- and sex-specific norms[32], with a higher score indicating better HRQoL. Impairment was defined as a *T*-score falling at least one SD below the normative mean of 50.

Data on social attainment were examined for those participants who were older than 25 years at the most recent available follow-up time point. This data included highest educational attainment (college graduate and above vs. below), employment status (categorized as full-time employment vs. others), annual household income (≤20,000

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vs. >20,000 US dollars), current marital status (ever-married vs. never-married), and independent living status.

Predictors and covariates

The predictor of interest in this study is race (API vs NHW). The other covariates included sex, race, age at completion of survey, age at diagnosis and original cancer diagnosis. Treatment variables included intrathecal (IT) methotrexate (yes vs. no), intravenous (IV) methotrexate (yes vs. no) and cranial radiation (CRT) dose. All treatment exposures (radiation and chemotherapy) were abstracted from the medical records of treating institutions. Cranial radiation maximum target dose was determined based on a detailed review of radiation therapy records and taken as the sum of the prescribed dose from all overlapping brain fields.

Chronic health conditions were graded for severity according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, [33] using previously reported methods.[6,7,18,20] Survivors reported their organ-specific chronic health conditions and age at onset at baseline and at subsequent follow-up evaluations. For this study, the health conditions of interest were limited to cardiovascular, pulmonary, endocrine, and neurological systems, in accordance with evidence from literature and previous CCSS reports supporting an association of these chronic health conditions with functional outcomes in survivors. [6,7,18,20]

Statistical analysis

Descriptive analyses were performed to summarize the distributions of the outcome variables and covariates according to groupings consistent with previous CCSS publications. Univariate analyses (Chi-square test for categorical variables and t-test for continuous variables) were conducted to compare baseline characteristics between API survivors *versus* NHW survivors.

Proportions of survivors and siblings with functional impairment within the API and NHW are presented for descriptive purposes. All subsequent comparison of the neurocognitive, emotional and HRQoL outcomes was conducted in the form of continuous *T*-scores. To ascertain the effect of cancer and treatment on functional outcomes in the API group, neurocognitive function (CCSS-NCQ), emotional distress (BSI-18), and HRQoL (SF-36) scores were analyzed within the API survivors using multiple linear regression, adjusted for sex, age at diagnosis and age at evaluation as a basic model. Then cancer diagnosis groups and treatment variables (IV methotrexate, IT methotrexate and CRT dose) were added to the basic model in two separate steps, to examine the effects of cancer diagnosis and treatment respectively. These two sets of cancer-related variables are highly correlated and could not be added together in a single model. The assumptions of linear models were checked and no violation was detected.[34] Comparison between API survivors and siblings were done in a single model adjusted for sex and age and evaluation. Modifications of the linear models by generalized estimating equations (GEE) were used to account for possible within-family correlation between survivors and siblings from the same family. Estimates of regression coefficients and 95% confidence intervals (CIs) were reported. The

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social attainment outcomes (employment, marital status, education attainment, household income, and independent living) were compared between the survivors and siblings of API using logistic regression with the GEE modifications, after adjusting for sex and the age at evaluation. Estimates of odds ratios (ORs) and 95% CIs are reported. Comparison of functional outcomes was not conducted among NHW survivors versus NHW siblings as this data was presented in a previous publication.[22]

To evaluate the effect of race on functional outcomes, multiple linear regression was used to compare the *T*-score outcomes between the survivors of API and NHW, adjusting for sex, age at evaluation, and treatment variables (IV methotrexate, IT methotrexate and CRT dose).

Lastly, the same regression methods were used to identify clinical and treatment factors associated with the *T*-score outcomes among the API survivors, after adjusting for sex and the age at evaluation. Clinical variables included cancer diagnosis groups and age at diagnosis, and treatment variables included the IV and IT methotrexate and CRT doses. CRT dose was categorized as five levels (None, <18Gy, 18 to 23.9 Gy, 24 to 49.9 Gy, and ≥50 Gy) based on its distribution. These variables were identified *a priori* because previous studies have suggested that the factors associated with poor functional outcomes in childhood cancer survivors include female sex, CNS tumor diagnosis, younger age at diagnosis, IV and IT methotrexate and higher CRT doses.[7,15–20] All analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC, USA). A *P* value of < .05 was considered statistically significant, and all tests were 2-sided.

Data availability

Raw data for this study were generated at the data repository of the Childhood Cancer Survivor Study (https://ccss.stjude.org/). Derived data supporting the findings of this study are available from the corresponding author upon request.

Results

Characteristics of the study cohort

A total of 203 API survivors and 31 API siblings and 12,186 NHW survivors and 2,908 NHW siblings completed the baseline and follow-up questionnaires (Table 1). The mean age at diagnosis was 7.0 (SD=5.4) years for API survivors and 7.9 (SD=5.8) years for NHW survivors (*P*=.036). The mean age at assessment for API survivors (29.2 [SD=6.3] years) was slightly younger than that of NHW survivors (31.5 [SD=7.3] years) (*P*<.001).

The proportion of leukemia survivors was higher in the API group (46.3%) than the NHW group (37.0%) (*P*=.009). The proportions of survivors diagnosed with CNS tumor were similar, 14.6% and 15.5% in API and NHW survivors, respectively. A higher proportion of API survivors received IV methotrexate (36.5% vs 25.8%; *P*<.001) and IT methotrexate (46.8% vs 38.4%; *P*=.008), as compared to NHW survivors. API survivors were also treated with marginally higher mean doses of IV methotrexate (42.4 [SD=70.2] g/m^2), as compared to NHW survivors (27.3 [SD=63.9] g/m^2) (*P*=0.09). API survivors also received higher doses of IT methotrexate than NHW survivors (216.1 [SD=134.6] mg/m^2 vs 166.6

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[SD=145.2] mg/m^2; *P*=0.006). API and NHW survivors received similar doses of CRT (*P*=0.89).

The most commonly reported moderate-to-severe chronic health condition was endocrine (API: 15.9% and NHW: 20.7%; *P*=.07) complications. There was significantly higher proportion of NHW survivors who reported moderate-to-severe cardiovascular conditions, as compared to API survivors (18.1% vs 10.2%; *P*<.001). None of the API and NHW siblings reported any moderate-to-severe chronic health conditions. As the proportion of API survivors and siblings who reported chronic health conditions was small, we did not include chronic health conditions as a predictor in subsequent analyses.

Neurocognitive function

After adjusting for sex and the age at evaluation, no difference was observed in neurocognitive outcomes between API survivors and siblings (Supplementary Table 1), as well as between API and NHW survivors (Table 2). Descriptively, more than a quarter of the survivors reported impairments in task efficiency (API: 30.6%, NHW: 24.7%) and memory (API: 32.1%, NHW: 25.3%) (Table 2).

Within the API group, survivors of CNS tumors reported more problems than did survivors of non-CNS solid tumors with task efficiency (Difference estimate [Est]=10.23, 95% CI=3.23, 17.24; *P*=.004) and memory (Est=11.64, 95% CI=5.40, 17.88; *P* < .001), after adjusting for sex and the age at evaluation (Table 3). Higher CRT doses were associated with poorer task efficiency and memory, and IV methotrexate was associated with poorer task efficiency (Table 3). Female survivors reported more emotional dysregulation than male survivors (Est=4.40, 95% CI=0.27, 8.52; *P*=.037). Survivors older than 45 years reported more emotional dysregulation (Est=12.10, 95% CI=4.94, 19.27; *P*=.001) and memory problems (Est=9.91, 95% CI=2.01, 17.81; *P*=.014) than younger survivors.

Emotional distress

No difference was observed for emotional distress between API survivors and siblings (Supplementary Table 1). The proportion of API survivors and siblings reporting depressive symptoms was 10.9% and 3.3%, respectively. We also did not identify differences in the level of emotional distress between API and NHW survivors.

Among API survivors, female survivors reported more somatization problems than male survivors (Est=2.93, 95% CI=0.26, 5.61; *P*=.031), after adjusting for sex and the age at evaluation (Supplementary Table 2).

HRQoL

API survivors reported worse physical function than their sibling controls (52.13 [SD=8.32] vs 55.06 [SD=2.10]; *P*=.016) (Supplementary Table 1). Interestingly, siblings (51.99 [SD=9.45]) reported more pain than survivors (54.11 [SD=8.98]) (*P*=.034). No difference was observed for other HRQoL outcomes between the API survivors and siblings.

API survivors reported, on average, less bodily pain than NHW survivors (54.11 [SD=8.98] vs 51.32 [SD=10.12]; *P*<.001) (Table 2). Up to a fifth of the survivors reported impaired

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general health (API: 21.8%, NHW: 22.6%), poor vitality (API: 17.1%, NHW: 22.1%), and pain (API: 10.2%, NHW: 16.1%).

An older age (>45 years) was associated with a worse HRQoL in terms of performance function, physical role, bodily pain, vitality, social functioning, and mental health in API survivors (all, $P<.05$) (Table 4). IV methotrexate was associated with poor physical functioning (Est= −2.84, 95% CI= −4.95, −0.74=1.07, $P=.008$), vitality (Est= −3.36, 95% CI= −6.66, −0.05; $P=.046$) and role emotional functioning (Est= −5.46, 95% CI= −9.79, −1.13; $P=.014$) (Table 4). Interestingly, survivors treated with IT methotrexate had better physical functioning (Est=4.12, 95% CI=2.01, 6.22; $P=.001$), vitality (Est=4.40, 95% CI=0.85, 7.96; $P=.015$), and less bodily pain (Est=4.06, 95% CI=1.09, 7.03; $P=.007$) than survivors who were not treated with IT methotrexate.

Social attainment

No difference was observed for social attainment between API survivors and siblings (Supplementary Table 1). The proportion of survivors (63.5%) who attained at least a college degree was lower than the sibling group with marginal statistical significance (77.5%, $P=.06$).

NHW survivors were less likely than API survivors to attain at least a college degree (OR=0.50, 95% CI=0.34, 0.73; $P<.001$) (Figure 1). API survivors (58.5%) were more likely than NHW survivors (35.8%) to be never married (OR=2.83, 95% CI=1.93, 4.13; $P<.001$). API survivors (39.2%) were three times more likely than NHW survivors (17.9%) to live dependently (OR=3.10, 95% CI=2.02, 4.74; $P<.001$).

API survivors who were diagnosed at a younger age (0–4 years) were more likely to be never-married and less likely to live independently than older survivors (all, $P<.05$) (Table 5). Compared to survivors of non-CNS solid tumors, survivors of CNS tumors were at elevated risk of not completing a college education (OR=2.69, 95% CI=1.12, 6.42; $P=.026$) and living dependently (OR=3.01, 95% CI=1.09, 8.28; $P=.033$).

Discussion

Our study identified no overall statistically significant differences in neurocognitive problems, emotional distress, and HRQoL outcomes between API and NHW survivors. The clinical and treatment factors associated with functional outcomes in this study were largely similar to those that are well-established in the literature, suggesting that these functional outcomes were primarily driven by the cancer and treatment exposures. After adjusting for age, sex, and treatment, API survivors were two times more likely than NHW survivors to complete a college education, but were less likely to be married or live independently. Consistent with observations across the general population in the United States, the differences in education achievement and social attainment between API and NHW survivors may likely be influenced by latent environmental and sociocultural factors.

We did not observe statistically significant differences in the neurocognitive functioning scores between API and NHW survivors. However, it is worth mentioning that close

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to a third of the API survivors reported impairments in task efficiency and memory, approximately 20% higher than the proportion of impairment in NHW survivors. Although the current analysis lacked power to detect statistical differences, such a substantial effect size found between API and NHW survivors suggests a potential clinically relevant disparity in neurocognitive outcomes and hence warrant a more comprehensive investigation using a combination of self-report and objective testing. We also identified an older age, CNS tumor diagnosis, and higher doses of cranial radiation as associated with worse neurocognitive function and HRQoL in API survivors. These findings are consistent with those of worse health and functional outcomes in previous CCSS reports and in the literature[16,17], indicating that clinical and treatment exposures are strong determinants of long-term functional outcomes. These subgroups of high-risk survivors, regardless of race and ethnicity, warrant closer monitoring and targeted interventions to improve their functional outcomes.

API survivors had higher levels of education attainment and were two times more likely than NHW survivors to complete a college education. This observation is consistent with studies in the general population, which have shown that regardless of cognitive abilities or socio-demographics factors, Asian Americans attain college education more than NHW due to higher expectations of academic achievement.[35] Similarly, cultural factors might explain why a higher proportion of NHW survivors were married and lived independently, as compared to API survivors. In the United States, adult Asian-Americans are more likely than Whites to reside with family members within multigenerational households because they tend to assume responsibility in providing care for elderly parents.[36] A recent report also showed that the proportion of never-married Asian-Americans had increased from 13% in 1980 to 19% in 2012 for various reasons, including the higher prioritization of education, career development, or life choices.[37] Therefore, researchers should note that such indicators are substantially confounded by sociocultural factors and may not be accurate markers of differential functional independence in the API population. Collectively, these observations demonstrate the complex relationships between racial and sociocultural factors when examining functional attainment in childhood cancer survivors.

The influence of sociocultural factors should be considered when interpreting the results. For example, we found that API survivors reported less bodily pain than NHW survivors. This finding should not instinctively lead to the conclusion that API survivors suffer less pain than NHW survivors because the expression of distressing emotions, including cancer pain and psychological stress, tends to be suppressed in many Asian cultures.[38] Although the current analysis does not take into account the influence of sociocultural factors, future studies should examine other predictors of functional outcomes that might be influenced by race and ethnicity, including risky health behaviors, healthcare utilization patterns, and family functioning.[26,39–42] For example, psychological stress has been associated with risky health behaviors (e.g., tobacco use, risky alcohol use, physical inactivity) in survivors of childhood cancer, and non-White race/ethnicity has been identified as a risk factor.[43] However, given the small proportion of API survivors in most studies, non-Hispanic black survivors most likely dominated the minority group. In the general United States population, the prevalence of cigarette smoking is lower among API adults than among other racial ethnic groups.[44] Notably, there are differential patterns of health

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behaviors even among Asian Americans; for example, tobacco use is highest among those of Korean and Vietnamese ethnicity, compared to those of Chinese and Indian ethnicity.[45,46] Consequently, the presentation of functional impairment and psychosocial outcomes may differ among API survivors. This possibility emphasizes the need to understand ethnic differences and consider sociocultural factors in long-term survivorship experiences among Asian-American subgroups. Future studies should include collection of data on health behaviors, sociocultural environment and healthcare system factors (medical insurance coverage and accessibility to quality survivorship care) so that we can further identify the relevant levels of intervention that are required to reduce cancer health disparities.

Our findings may lay a foundation for future multinational and multiracial research in the growing population of Asian childhood cancer survivors. We acknowledge that the outcomes evaluated in Asian-American survivors cannot be extrapolated to survivors on the Asian continent, due to potential differences in treatment regimens, healthcare systems, and lifestyle factors.[47] However, our findings from Asian-Americans may justify the need for the investigation of such outcomes in Asia, which is projected to face an emerging population of childhood cancer survivors in the next decades. Currently, the few studies that have evaluated functional outcomes in native Asian survivors have yielded inconclusive results.[47,48] Compared with healthy controls, childhood cancer survivors in South Korea reported significantly lower physical and psychosocial HRQoL scores.[49] However, HRQoL and emotional distress did not differ considerably between Chinese survivors and sibling controls in Hong Kong.[50] Another Japanese study also revealed no significant differences in depression and anxiety between survivors and their siblings, though survivors exhibited higher levels of post-traumatic stress symptoms and post-traumatic growth than non-cancer unrelated controls.[51] A recently published systematic review reported that 10.0%–42.8% of Asian survivors of childhood cancer in Japan, South Korea, Taiwan, Hong Kong, and Thailand demonstrated mild-to-moderate impairments in intelligence (overall IQ).[48] These differences in neurocognitive and psychological functioning between Asian ethnic groups emphasize the need to tailor behavioral and psychological interventions in multi-ethnic communities. The comparison of outcomes between API survivors in the United States and in Asia would also yield novel information about the interacting effects of genetic, region-specific environmental, and sociocultural factors on late effects and functional outcomes in cancer survivors.

Our study has the following limitations. Given the small sample of API siblings, our analysis might not be sufficiently powered to detect statistical differences in outcomes between survivors and siblings as observed in other published reports on the overall CCSS population[6,7,12,52], though descriptively, the prevalence of impairment in task efficiency, memory and depression seemed higher in API survivors than API siblings. Consistent with other CCSS publications[22,28], there is a higher proportion of siblings is in the NHW group (19.3%) than the API group (13.2%), leading to potential selection bias. The sample size was also too small to allow other potentially meaningful analyses, such as an evaluation of differences in chronic health conditions between API and NHW survivors and a subgroup analysis stratified by treatment exposure (e.g., CRT). However, to the best of our knowledge, this is the largest study to evaluate functional outcomes in API survivors of childhood cancer in the United States and to include the detailed cancer therapy history and

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non-cancer siblings as comparators. The association analysis of functional outcomes might be confounded by cancer diagnoses and treatment variables. For example, IT methotrexate chemotherapy was associated with better task efficiency and multiple HRQoL measures, possibly because IT methotrexate chemotherapy is inversely related to use and dose of CRT therapy in survivors of acute lymphoblastic leukemia (ALL) and CNS tumors, i.e., those ALL survivors who did not receive IT methotrexate likely received CRT and CNS tumor survivors typically do not receive IT methotrexate.[17,53]

Investigations of racial and ethnic disparities in cancer survivorship have become increasingly important. In conclusion, we found differences in social attainment between API and NHW survivors, although statistically significant disparity in long-term neurocognitive and emotional outcomes were not identified. Consistent with the literature, API survivors of CNS tumors and survivors treated with higher CRT doses had a higher risk of poorer neurocognitive function and a worse HRQoL. Future studies should evaluate racial/ethnic differences in environmental and sociocultural factors among API survivors and how these may have differential effects on health and functional outcomes. From a clinical perspective, unveiling the contributors to racial/ethnic differences in functional outcomes will pave the way for the development of targeted interventions to mitigate these differences. The eventual goal is to develop or expand ongoing culturally and linguistically tailored interventions to address modifiable factors in at-risk groups, such as programs to improve social functioning and functional independence in API survivors of CNS tumors or those diagnosed with cancer at a younger age. Efforts should be made to promote health equity by race and ethnicity among all survivors of childhood cancer in the United States.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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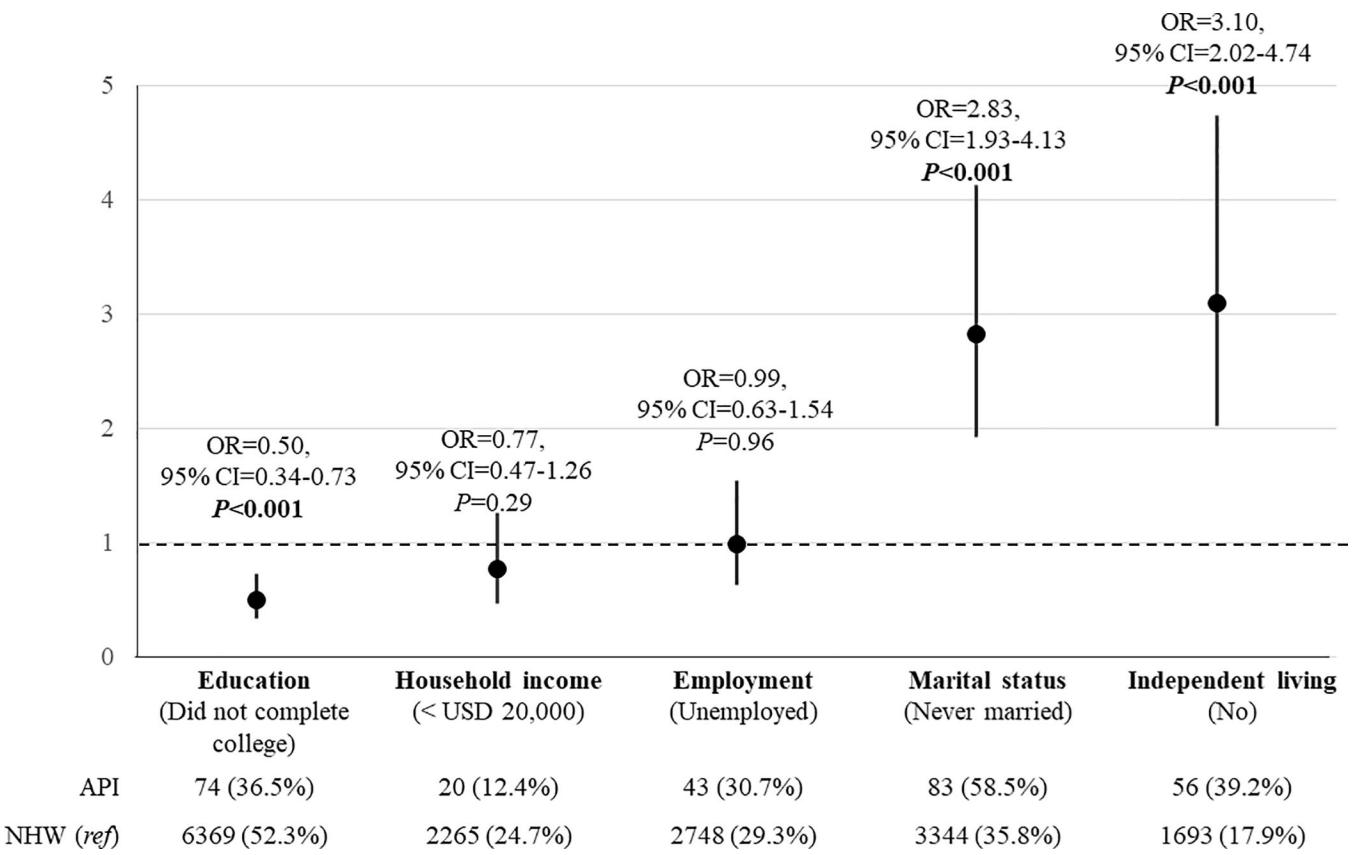

Figure 1:

Comparison of Social Attainment Asian/ Pacific Islander and non-Hispanic White Survivors

API: Asian or Pacific Islander; CI: confidence interval; NHW: non-Hispanic White; OR: odds ratio; ref: reference group

Adjusted for sex and age at evaluation, and treatment variables (intrathecal methotrexate, intravenous methotrexate, cranial radiation dose).

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Table 1:

Baseline Demographic and Clinical Characteristics

	Survivors			Siblings	
	API	**NHW**	***P*** ¶	**API**	**NHW**
N (%)	203 (1.3)	12,186 (79.5)		31 (0.2%)	2,908 (19.0)
Sex			0.25		
Male	95 (46.2)	6095 (49.9)		13 (41.9)	1325 (45.6)
Female	108 (53.8)	6091 (50.1)		18 (58.1)	1583 (54.4)
Age at assessment * (years)	29.2 (6.3)	31.5 (7.3)	**<0.001**	28.9 (6.7)	33.5 (8.8)
Health Insurance			0.14		
Yes	189 (94.3)	10933 (89.8)		31 (100.0)	2654 (91.3)
No	12 (4.9)	1165 (9.5)		0 (0.0)	241 (8.3)
Not specified	2 (0.8)	88 (0.7)		0 (0.0)	13 (0.4)
Diagnosis			**0.009**		
Leukemia	71 (46.3)	3691 (37.0)			
CNS tumor	36 (14.6)	2092 (15.5)			
Others (non-CNS solid tumors)	96 (39.0)	6403 (47.5)			
Age at Diagnosis * (years)	7.0 (5.4)	7.9 (5.8)	**0.036**		
Chemotherapy					
Anthracycline	99 (53.5)	5117 (48.3)	0.10		
Alkylating Agent	110 (52.6)	5898 (51.5)	0.28		
IV Methotrexate	55 (36.5)	2455 (25.8)	**<0.001**		
Cumulative dose (g/m^2) #	42.4 (70.2)	27.3 [63.9]	0.09		
IT Methotrexate	69 (46.8)	3651 (38.4)	**0.008**		
Cumulative dose (mg/m^2) #	216.1 (134.6)	166.6 (145.2)	**0.006**		
Anti-tumor Antibiotic	38 (16.0)	2588 (20.3)	0.10		
Corticosteroids	83 (51.6)	4784 (46.7)	0.13		
Enzymes	54 (39.3)	2801 (31.0)	**0.007**		
Epipodophyllotoxins	42 (20.8)	1784 (18.5)	0.48		
Heavy Metals	37 (15.5)	1036 (8.1)	**<0.001**		
Plant Alkaloids	116 (66.5)	7566 (69.1)	0.39		
Radiation					
Chest radiation	39 (16.8)	2862 (23.4)	**0.017**		
Abdomen radiation	42 (18.0)	2662 (21.8)	0.17		
Pelvic radiation	32 (13.7)	2203 (18.1)	0.09		
Cranial radiation	61(29.7)	3425 (29.5)	0.96		
Cranial radiation dose (Gy) €			0.89		
None	130 (68.4)	7871 (69.9)			
<18 Gy	10 (5.3)	256 (2.3)			

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	Survivors			Siblings	
	API	NHW	*P* ¶	API	NHW
18 – 23.9 Gy	17 (9.0)	951 (8.4)			
24 – 49.9 Gy	13 (6.8)	1163 (10.3)			
≥50 Gy	20 (10.5)	1029 (9.1)			
Chronic Health Conditions (Grade) *					
Cardiovascular			**0.001**		
None or Mild	178 (89.8)	9915 (81.9)		31 (100.0)	2908 (100.0)
Moderate or Severe/life-threatening	25 (10.2)	2271 (18.1)		0 (0.0)	0 (0.0)
Pulmonary			0.83		
None or Mild	193 (95.9)	11646 (95.6)		31 (100.0)	2908 (100.0)
Moderate or Severe/life-threatening	10 (4.1)	540 (4.4)		0 (0.0)	0 (0.0)
Endocrine			0.07		
None or Mild	167 (84.1)	9656 (79.3)		31 (100.0)	2908 (100.0)
Moderate or Severe/life-threatening	36 (15.9)	2530 (20.7)		0 (0.0)	0 (0.0)
Neurologic			0.78		
None or Mild	181 (91.0)	11187 (91.5)		31 (100.0)	2908 (100.0)
Moderate or Severe/life-threatening	22 (9.0)	999 (8.5)		0 (0.0)	0 (0.0)

API: Asian/Pacific Islanders; CNS: central nervous system; NHW: non-Hispanic Whites; IT: intrathecal; IV: intravenous

¶Comparisons between survivors of API *versus* NHW survivors

#Presented as a continuous variable: mean (standard deviation)

*Chronic health conditions were graded for severity according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 4.03). "None or mild" refers to Grades 0 and 1 conditions while "moderate or severe/ life-threatening" refers to Grades 2 to 4 conditions.

€Cranial radiation dose is the maximum target dose, which was taken as the sum of the prescribed doses from all overlapping brain radiation fields.

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Table 2:

Comparison of Functional Outcomes in Asian/ Pacific Islander and Non-Hispanic White Survivors

	Asian/ Pacific Islander		Non-Hispanic White		Comparison of *T*-scores[§]		
	Mean (SD)	**% impaired**	**Mean (SD)**	**% impaired**	**Est.**	**95%CI**	***P***
Neurocognitive function [*]	n=175		n=10,479				
Task Efficiency	56.23 (15.16)	30.6	54.73 (14.06)	24.7	0.91	(−1.79, 3.61)	0.51
Emotional Regulation	50.33 (11.79)	17.1	52.15 (11.10)	19.0	−1.57	(−3.92, 0.78)	0.19
Organization	51.32 (10.44)	12.7	51.18 (10.92)	12.8	−0.31	(−2.03, 1.41)	0.72
Memory	54.13 (13.27)	32.1	53.28 (12.33)	25.3	0.82	(−1.49, 3.13)	0.49
Emotional status [‡]	n=164		n=9803				
Anxiety	45.64 (9.13)	5.5	46.97 (9.26)	7.4	−1.05	(−2.97, 0.87)	0.29
Depression	48.09 (9.70)	10.9	48.55 (9.50)	11.1	−0.02	(−2.00, 1.96)	0.99
Somatization	47.89 (7.99)	6.1	49.42 (8.74)	11.4	−1.04	(−2.47, 0.39)	0.15
Health-related quality of life [†]	n=198		n=12001				
Performance Function	52.13 (8.32)	12.2	51.42 (9.40)	11.7	0.35	(−0.67, 1.37)	0.50
Role Physical	52.04 (9.21)	12.2	50.97 (9.77)	13.9	0.85	(−0.52, 2.22)	0.23
Bodily Pain	54.11 (8.98)	10.2	51.32 (10.12)	16.1	2.48	(1.17, 3.79)	**<0.001**
General Health	48.74 (10.76)	21.8	48.52 (11.31)	22.6	−0.51	(−2.49, 1.47)	0.62
Vitality	50.37 (9.64)	17.1	48.96 (10.33)	22.1	1.15	(−0.46, 2.76)	0.16
Social Functioning	49.79 (9.95)	15.2	50.15 (10.38)	14.3	−0.17	(−1.70, 1.36)	0.82
Role Emotional	49.81 (11.37)	17.4	50.37 (10.10)	16.0	−0.47	(−2.31, 1.37)	0.62
Mental Health	50.16 (10.31)	18.2	49.88 (9.96)	17.2	0.06	(−1.65, 1.77)	0.94
Social attainment							
	n	**%**	**n**	**%**	**OR**	**95% CI**	***P***
Education level:							
Below college graduate	74	36.5	6359	52.3	0.50	(0.34, 0.73)	**<0.001**
College graduate and above	129	63.5	5794	47.7			
Household income							
< 20,000	20	12.4	2265	24.7	0.75	(0.45, 1.24)	0.26
≥ 20,000	142	87.6	6908	75.3			
Employment status							
Unemployed	43	30.7	2748	29.3	0.96	(0.60, 1.52)	0.86
Employed/ Student	97	69.3	6617	70.7			
Current marital status							
Ever married	59	41.5	6008	64.2			
Never married	83	58.5	3344	35.8	2.83	(1.94, 4.12)	**<0.001**
Independent living							
Yes	87	60.8	7742	82.1			
No	56	39.2	1693	17.9	3.12	(2.02, 4.80)	**<0.001**

CNS: central nervous system; CI: confidence interval; Est: estimate; OR: odds ratio; SD: standard deviation

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[§] The comparison between API and NHW survivors was conducted using the continuous *T*-scores as the primary outcome. Models were adjusted for sex, age at evaluation and treatment variables (intrathecal methotrexate, intravenous methotrexate and cranial radiation dose). Non-Hispanic White survivors were assigned as the referent group.

[*] Neurocognitive function referred to scores on the Neurocognitive Questionnaire (NCQ). A higher score indicates more cognitive problems. Impaired performance was defined as a score falling ≥90th percentile based on values obtained in the sibling cohort

[‡] Emotional status referred to scores on the Brief Symptom Inventory (BSI-18). A higher score indicates more symptoms. Significant distress will be defined as T-scores ≥ 63 (*90th percentile*) for each subscale.

[†] Health-related quality of life referred to scores on the Short-form 36 (SF-36). A higher score indicates better quality of life. Impairment was defined as a score falling below a T-score of 40 (1 standard deviation below the mean)

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Table 3:

Factors Associated with Neurocognitive Function in Asian/ Pacific Islander Survivors

	Task Efficiency		Emotional Regulation		Organization		Memory	
	Est (95% CI) †	***P***	**Est (95% CI)** †	***P***	**Est (95% CI)** †	***P***	**Est (95% CI)** †	***P***
Demographic variables §								
Sex								
Male (referent)	--	--	--	--	--	--	--	--
Female	−1.52 (−6.90, 3.87)	0.58	4.40 (0.27, 8.52)	**0.037**	−3.03 (−6.44, 0.39)	0.08	1.31 (−3.17, 5.78)	0.57
Age at evaluation (years)								
<25 (referent)	--	--	--	--	--	--	--	--
25–34	0.99 (−5.47, 7.46)	0.76	7.13 (1.24, 13.01)	**0.018**	−2.14 (−6.46, 2.18)	0.33	1.83 (−3.57, 7.22)	0.51
35–44	4.08 (−4.68, 12.85)	0.36	5.22 (−1.97, 12.41)	0.15	0.31 (−6.33, 6.94)	0.93	−0.94 (−8.66, 6.78)	0.81
≥45	5.31 (−3.61, 14.24)	0.24	12.10 (4.94, 19.27)	**0.001**	3.19 (−4.34, 10.72)	0.41	9.91 (2.01, 17.81)	**0.014**
Age at diagnosis (years)								
0–4 (referent)	--	--	--	--	--	--	--	--
5–9	1.61 (−5.97, 9.20)	0.68	−2.65 (−8.80, 3.49)	0.40	1.68 (−2.59, 5.95)	0.44	3.60 (−2.78, 9.97)	0.27
10–14	2.55 (−5.28, 10.37)	0.52	0.09 (−6.87, 7.05)	0.98	4.62 (−0.59, 9.84)	0.08	6.54 (−0.75, 13.82)	0.08
15–18	−2.64 (−11.50, 6.22)	0.56	−5.29 (−13.04, 2.46)	0.18	−0.89 (−8.00, 6.21)	0.81	3.78 (−3.47, 11.02)	0.31
Cancer diagnosis *								
Non-CNS solid tumors (referent)	--	--	--	--	--	--	--	--
Leukemia	4.46 (−1.24, 10.16)	0.13	2.64 (−1.98, 7.26)	0.26	−1.18 (−4.72, 2.35)	0.51	4.69 (0.12, 9.26)	**0.044**
CNS tumor	10.23 (3.23, 17.24)	**0.004**	2.99 (−1.64, 7.61)	0.21	4.12 (−0.87, 9.11)	0.11	11.64 (5.40, 17.88)	**<0.001**
Treatment variables ‡								
Chemotherapy								
IT Methotrexate								
No (referent)	--	--	--	--	--	--	--	--
Yes	−9.30 (−15.33, −3.27)	**0.003**	−3.41 (−8.25, 1.43)	0.17	−4.16 (−8.16, −0.15)	**0.042**	−4.34 (−9.65, 0.97)	0.11
IV Methotrexate								
No (referent)	--	--	--	--	--	--	--	--

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	Task Efficiency		Emotional Regulation		Organization		Memory	
	Est (95% CI) †	***P***	**Est (95% CI)** †	***P***	**Est (95% CI)** †	***P***	**Est (95% CI)** †	***P***
Yes	5.84 (0.52, 11.17)	**0.031**	2.19 (−2.95, 7.33)	0.40	−0.70 (−4.40, 3.00)	0.71	2.57 (−2.11, 7.24)	0.28
Cranial Radiation								
None (referent)								
<18 Gy	9.71 (1.62, 17.80)	**0.019**	12.12 (5.99, 18.26)	**<0.001**	0.80 (−5.12, 6.71)	0.79	9.38 (0.79,17.98)	**0.032**
18 – 23.9 Gy	14.25 (3.32, 25.18)	**0.011**	2.92 (−4.57, 10.41)	0.44	5.71 (−0.08, 11.49)	0.053	8.79 (1.07–16.51)	**0.026**
24 – 49.9 Gy	6.20 (−3.22, 15.62)	0.20	2.19 (−4.42, 8.80)	0.52	2.26 (−4.06, 8.59)	0.48	1.87 (−5.73, 9.47)	0.63
≥50 Gy	8.75 (0.08, 17.42)	**0.048**	1.40 (−4.24, 7.05)	0.63	0.93 (−4.91, 6.78)	0.75	9.18 (1.37, 17.00)	**0.021**

CNS: central nervous system; Est: estimate; IT: intrathecal; IV: intravenous; 95% CI: 95% confidence interval

†Refers to estimate of the difference in scores. A positive estimate indicates that the group with the variable of interest reported more problems than the referent group.

Outcomes were analyzed adjusting for

§demographic variables

*demographic variables and cancer diagnoses; and

ǂdemographic variables and treatment variables

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Table 4:

Factors Associated with Health-related Quality of Life in Asian/ Pacific Islander Survivors

	Physical Function		Role Physical		Bodily Pain		General Health		Vitality		Social Functioning		Role Emotional		Mental Health	
	Est (95% CI)	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***
Demographic variables [§]																
Sex																
Male (ref)	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Female	−1.02 (−2.92, 0.87)	0.29	−1.98 (−4.53, 0.58)	0.13	−0.92 (−3.48, 1.65)	0.49	−1.98 (−5.61, 1.66)	0.29	0.02 (−2.96, 3.00)	0.99	−0.73 (−3.60, 2.14)	0.62	0.56 (−2.84, 3.96)	0.75	−0.78 (−3.94, 2.38)	0.63
Age at evaluation (years)																
< 25 (ref)	--	--	--	--			--	--	--	--						
25–34	0.40 (−1.76, 2.56)	0.72	0.21 (−3.01, 3.44)	0.90	−0.68 (−4.04, 2.69)	0.69	−5.95 (−10.73, −1.18)	**0.015**	−0.75 (−4.98, 3.48)	0.73	−1.91 (−5.87, 2.05)	0.34	1.23 (−3.25, 5.72)	0.59	−2.11 (−6.45, 2.24)	0.34
35–44	2.85 (−1.73, 7.42)	0.22	1.15 (−3.78, 6.08)	0.65	−0.32 (−5.74, 5.10)	0.91	−1.70 (−8.38, 4.99)	0.62	3.21 (−2.57, 8.99)	0.28	2.87 (−2.66, 8.40)	0.31	2.36 (−4.29, 9.01)	0.49	2.59 (−3.75, 8.94)	0.42
≥45	8.74 (3.40, 14.07)	**0.001**	6.03 (0.62, 11.44)	**0.029**	−7.47 (−13.68, −1.27)	**0.018**	6.27 (−0.71, 13.25)	0.08	21.57 (15.63, 27.51)	**<0.001**	6.57 (0.92, 12.22)	**0.023**	−1.83 (−8.38, 4.72)	0.58	9.35 (2.62, 16.08)	**0.006**
Age at diagnosis (years)																
0–4 (ref)	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
5–9	−1.70 (−4.33, 0.93)	0.21	0.80 (−1.86, 3.47)	0.55	−0.35 (−3.78, 3.08)	0.84	2.29 (−2.63, 7.20)	0.36	−0.84 (−5.15, 3.46)	0.70	0.70 (−3.36, 4.76)	0.74	−0.19 (−4.40, 4.01)	0.93	0.62 (−3.92, 5.16)	0.79
10–14	−7.34 (−11.24, 3.44)	**<0.001**	−3.25 (−7.84, 1.35)	0.17	−3.87 (−8.31, 0.57)	0.088	−2.07 (−8.05, 3.91)	0.50	−4.91 (−10.18, 0.37)	0.07	−4.27 (−9.83, 1.30)	0.13	−4.02 (−10.11, 2.07)	0.20	−4.01 (−10.28, 2.27)	0.21
15–18	−6.62 (−11.53, −1.71)	**0.008**	−3.12 (−8.38, 2.14)	0.25	−3.25 (−9.25, 2.74)	0.29	−2.07 (−9.07, 4.92)	0.56	−2.61 (−8.04, 2.83)	0.35	−1.44 (−6.81, 3.94)	0.60	0.74 (−5.55, 7.02)	0.82	3.22 (−2.91, 9.35)	0.30

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	Physical Function		Role Physical		Bodily Pain		General Health		Vitality		Social Functioning		Role Emotional		Mental Health	
	Est (95% CI)	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***
Cancer diagnosis *																
Others (ref)	--	--	--	--			--	--	--	--						
Leukemia	0.85 (−0.97, 2.67)	0.36	1.73 (−0.93, 4.38)	0.20	1.38 (−1.29, 4.06)	0.31	−1.09 (−4.86, 2.69)	0.57	2.47 (−0.70, 5.64)	0.13	0.92 (−2.14, 3.98)	0.56	0.48 (−3.05, 4.02)	0.79	0.79 (−2.55, 4.12)	0.64
CNS tumor	−3.14 (−7.04, 0.77)	0.12	−0.07 (−3.54, 3.39)	0.97	0.19 (−3.62, 3.99)	0.92	−3.55 (−8.12, 1.02)	0.13	1.28 (−2.94, 5.51)	0.55	−2.08 (−6.13, 1.97)	0.32	−1.71 (−6.62, 3.20)	0.49	−2.14 (−6.48, 2.20)	0.33
Treatment variables †																
Chemotherapy																
IT Methotrexate																
No (referent)	--	--	--	--			--	--	--	--						
Yes	4.12 (2.01, 6.22)	**0.001**	3.42 (0.30, 6.53)	**0.031**	4.06 (1.09, 7.03)	**0.007**	0.17 (−4.19, 4.53)	0.94	4.40 (0.85, 7.96)	**0.015**	1.44 (−2.22, 5.10)	0.44	2.68 (−1.36, 6.71)	0.19	3.51 (−0.75, 7.76)	0.11
IV Methotrexate																
No (referent)	--	--	--	--			--	--	--	--						
Yes	−2.93 (−5.01, −0.84)	**0.006**	−2.44 (−5.51, 0.63)	0.12	−0.81 (−3.71, 2.09)	0.58	−1.05 (−5.12, 3.02)	0.61	−3.27 (−6.57, 0.03)	.052	−0.48 (−4.06, 3.10)	0.79	−5.45 (−9.75-, −1.16)	**0.013**	−1.04 (−5.22, 3.14)	0.62
Cranial Radiation ‖																
None (referent)	--		--		--		--		--		--		--		--	
<18 Gy	0.44 (−6.70, 7.59)	0.90	2.06 (−2.71, 6.84)	0.40	1.24 (−3.57, 6.05)	0.61	−5.79 (−10.98, −0.60)	**0.029**	−1.16 (−7.00, 4.67)	0.70	0.30 (−3.84, 4.43)	0.89	0.81 (−5.92, 7.53)	0.81	−0.28 (−7.49, 6.93)	0.94
18–23.9 Gy	−3.04 (−7.01, 0.92)	0.13	0.03 (−3.45, 3.51)	0.99	−7.34 (−11.39, −3.29)	**0.001**	0.30 (−4.48, 5.09)	0.90	−3.27 (−8.45, 1.90)	0.22	0.41 (−3.53, 4.36)	0.84	3.06 (−1.74, 7.85)	0.21	−0.03 (−3.86-, 3.81)	0.99
24–49.9 Gy	−0.58 (−4.57, 3.42)	0.78	−2.84 (−9.01, 3.33)	0.37	−0.74 (−6.39, 4.90)	0.80	−3.90 (−10.55, 2.76)	0.25	0.81 (−3.25, 4.87)	0.70	1.70 (−2.74, 6.14)	0.45	−0.88 (−7.72, 5.95)	0.80	2.38 (−1.96, 6.73)	0.28

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	Physical Function		Role Physical		Bodily Pain		General Health		Vitality		Social Functioning		Role Emotional		Mental Health	
	Est (95% CI)	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***	**Est (95% CI)**	***P***
≥50 Gy	−3.82 (−9.16, 1.52)	0.16	−0.81 (−4.58, 2.96)	0.67	0.09 (−4.63, 4.81)	0.97	−6.73 (−12.64, −0.81)	**0.026**	−0.09 (−5.14, 4.97)	0.97	−1.15 (−6.43, 4.14)	0.67	−1.61 (−7.03, 3.81)	0.56	−2.05 (−7.39, 3.30)	0.45

CNS: central nervous system; Est: estimate; IT: intrathecal; IV: intravenous; ref: referent; 95% CI: 95% confidence interval

†Refers to estimate of the difference in scores. A negative estimate indicates that the group with the variable of interest reported poorer quality of life than the referent group

Outcomes were analyzed adjusting for

§demographic variables

*demographic variables and cancer diagnoses; and

ǂdemographic variables and treatment variables

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Table 5:

Association of Factors with Social Attainment in Asian/ Pacific Islander Survivors

	Social Attainment									
	Education		Employment		Marital status		Independent living		Household income	
	Not completing college		Unemployed		Single, never married		No		<USD 20,000	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Demographic variables [§]										
Sex										
Male (referent)	--	--	--	--	--	--	--	--	--	--
Female	1.09 (0.53, 2.23)	0.82	2.95 (1.22, 7.17)	**0.017**	0.66 (0.29, 1.49)	0.32	1.56 (0.67, 3.59)	0.30	2.06 (0.80, 5.27)	0.13
Age at evaluation (years)										
<25 (referent)										
25–34	0.34 (0.14, 0.82)	**0.017**	--	--	--	--	--	--	--	--
35–44	0.14 (0.04, 0.51)	**0.003**	1.29 (0.49, 3.39)	0.61	0.42 (0.16, 1.10)	0.08	0.88(0.31, 2.49)	0.81	0.62 (0.21, 1.84)	0.39
Age at diagnosis (years)										
0–4 (referent)	--	--	--	--	--	--	--	--	--	--
5–9	0.84 (0.30, 2.33)	0.74	0.90 (0.27, 3.01)	0.87	0.20 (0.05, 0.75)	**0.017**	0.40 (0.14, 1.16)	0.09	1.27 (0.35, 4.66)	0.72
10–14	1.29 (0.45, 3.70)	0.63	1.10 (0.33, 3.73)	0.87	0.08 (0.02, 0.31)	**<0.001**	0.13 (0.04, 0.42)	**<0.001**	1.93 (0.53, 7.05)	0.32
15–18	0.86 (0.23, 3.20)	0.82	1.42 (0.35, 5.86)	0.63	0.07 (0.02, 0.29)	**<0.001**	0.20 (0.05, 0.82)	**0.025**	1.84 (0.38, 8.84)	0.45
Cancer diagnosis [*]										
Non-CNS solid tumor (referent)	--	--	--	--	--	--	--	--		
Leukemia	1.10 (0.50, 2.40)	0.81	1.29 (0.49, 3.40)	0.60	1.11 (0.43, 2.85)	0.83	0.77 (0.29, 2.05)	0.60	0.56 (0.17, 1.79)	0.33
CNS tumor	2.69 (1.12, 6.42)	**0.026**	1.96 (0.68, 3.40)	0.21	2.67 (0.87, 8.15)	0.09	3.01 (1.09, 8.28)	**0.033**	0.84 (0.29, 2.45)	0.75
Treatment variables [ǂ]										
Chemotherapy										
IT Methotrexate										
No (referent)	--	--	--	--	--	--	--	--	--	--
Yes	0.70 (0.28, 1.72)	0.44	1.30 (0.48, 3.53)	0.61	1.10 (0.38, 3.18)	0.86	0.40 (0.13, 1.22)	0.11	1.15 (0.43, 3.07)	0.78
IV Methotrexate										

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	Social Attainment									
	Education		Employment		Marital status		Independent living		Household income	
	Not completing college		Unemployed		Single, never married		No		<USD 20,000	
	OR (95% Cl)	*P*	OR (95% Cl)	*P*	OR (95% Cl)	*P*	OR (95% Cl)	*P*	OR (95% Cl)	*P*
No (referent)	--	--	--	--	--	--	--	--	--	--
Yes	0.72 (0.28, 1.81)	0.48	0.84 (0.31, 2.29)	0.74	0.69 (0.25, 1.88)	0.70	1.40 (0.47, 4.11)	0.54	0.71 (0.25, 2.01)	0.52
Cranial Radiation										
None	1.00 (1.00, 1.00)	--	1.00 (1.00, 1.00)	--	1.00 (1.00, 1.00)	--	1.00 (1.00, 1.00)	--	1.00 (1.00, 1.00)	--
<18 Gy	0.61 (0.14, 2.66)	0.52	--	--	1.99 (0.50, 7.90)	0.33	1.23 (0.17, 8.69)	0.83	--	--
18–23.9 Gy	0.87 (0.16, 4.75)	0.87	1.02 (0.23, 4.56)	0.97	3.34 (0.55, 20.47)	0.19	7.15 (1.52, 33.60)	**0.013**	0.87 (0.16, 4.83)	0.88
24–49.9 Gy	0.85 (0.23, 3.16)	0.81	6.37 (1.37, 29.59)	**0.018**	1.73 (0.29, 10.27)	0.55	2.02 (0.54, 7.59)	0.30	1.58 (0.34, 7.33)	0.56
≥50 Gy	1.65 (0.58, 4.63)	0.35	1.95 (0.56, 6.74)	0.29	3.82 (1.03, 14.21)	**0.046**	2.16 (0.70, 6.63)	0.18	0.41 (0.08, 2.06)	0.28

CI: confidence interval; CNS: central nervous system; IT: intrathecal; IV: intravenous; OR: Odds ratio

Outcomes were analyzed adjusting for

§ demographic variables

* demographic variables and cancer diagnoses; and

† demographic variables and treatment variables

For outcomes of employment and Independent living, categories of “<18 Gy” and “18–23.9 Gy” were combined to “<24 Gy” due to convergence issue.

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