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Neurocognitive impairment in Asian childhood cancer survivors: a systematic review

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Abstract

Childhood cancer survivors are at higher risk of developing neurocognitive deficits due to the intensive treatment they received at an early age. Most studies on childhood cancer survivorship have so far focused on the Western populations. Due to the ethnic, genetic, environmental, and cultural differences, clinical data of the Western populations may not be representative of Asian countries. This scoping review systematically summarized the existing clinical evidence of the neurocognitive impairment of Asian childhood cancer survivors. We searched the Embase and Medline databases for studies assessing the neurocognitive functions of survivors in Asia, who were diagnosed with cancer before the age of 19 and completed active treatment. The literature search identified 13 studies involving 2212 participants from five Asian countries: South Korea ($n = 4$, 30.8%), Taiwan ($n = 3$, 23.1%), Japan ($n = 3$, 23.1%), Hong Kong ($n = 2$, 15.4%), and Thailand ($n = 1$, 7.7%). The included studies focused on CNS tumors ($n = 10$, 76.9%), hematological malignancies ($n = 7$, 53.8%), or heterogeneous cancer diagnoses ($n = 3$, 23.1%). Collectively, mild-to-moderate impairment in intelligence was observed in 10.0 to 42.8% of survivors, which seemed higher than the reported rate in Western survivors. We speculate that the ethnic and genetic variations in drug responses and susceptibility to adverse chronic toxicities may have contributed to the differences in the prevalence and severity of neurocognitive impairment between these two populations. To better understand the effects of culturally relevant and region-specific environmental risk factors on the post-treatment neurocognitive development in cancer survivors, a holistic approach that addresses the complex interactions between biological, physical, and psychosocial factors is needed. This will aid the development of effective intervention strategies to improve the functional and psychosocial outcomes of cancer survivors in Asian societies.

Keywords Neurocognitive impairment · Chemotherapy · Childhood cancer survivors · Asia · Risk factors · Survivorship

1 Introduction

The incidence of childhood cancer is increasing worldwide. A recent study reported that between 1980s and 2000s, the global incidence of cancer in children aged 0–14 years has increased from 124.0 to 140.6 per million person-years [1]. As the most populated continent, Asia accounts for almost 50% of all registered cases of childhood cancer worldwide [2]. Although advancements in treatment modalities have improved the overall survival rates for childhood cancer in Asia [3–8], cancer survival is highly variable between countries and regions. In high-income Asian countries such as South Korea, Japan, Singapore, and Hong Kong, the overall survival rate for childhood cancer is approximately 80% [3–5, 9]. However, the survival rates of childhood cancer in many low- and middle-income countries (LMICs) in Asia can be as low as 20% [3, 6–8, 10].

Survivorship for childhood cancer is often associated with long-term treatment-related morbidities [11]. Notably, long-term childhood cancer survivors are at high risks of developing osteoporosis, secondary cancers, obesity, cardiovascular diseases, and cerebrovascular diseases [12–17]. Indeed, 66–88% of these long-term survivors suffer from at least one chronic condition later on in life, depending on the age of evaluation [18]. Other than physical late effects, social and

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academic problems, stress-related psychological disorders, and risky lifestyle behaviors are reported to be more prevalent in childhood cancer survivors than in healthy individuals [19–23].

Childhood cancer survivors are also at a high risk of developing neurocognitive deficits. These deficits may be caused by the cancer or the treatment received. Indeed, neurotoxic treatment modalities such as neurosurgery, cranial radiation (CRT), high-dose methotrexate, intrathecal chemotherapy, and corticosteroid treatments are known to be associated with severe neurocognitive impairment in childhood cancer survivors. Notably, demographic, social-environmental, and biological factors may also affect the neurodevelopment in childhood cancer survivors [24]. These neurocognitive problems can significantly affect the functional outcomes of the survivors later on in life, including education attainment, employment, income, and marital status [25].

Most studies on childhood cancer survivorship have so far focused on the Western populations. Due to the ethnic, genetic, environmental, and cultural differences, such as environmental contamination, lifestyle behaviors, and disparities in the healthcare systems, clinical data of the Western populations may not be representative of Asian countries [26]. Thus, there is an urgent need to generate clinical data on the neurocognitive outcomes in Asian childhood cancer survivors and explore the contributing factors for neurocognitive impairment in them. To address the abovementioned research gaps, this review aimed to summarize the existing evidence regarding the clinical ascertainment of neurocognitive impairment in Asian childhood cancer survivors. The findings of this review may help identify the etiological discrepancies between Western and Asian childhood cancer survivors and guide the development of future cognitive research and rehabilitation programs in Asia.

2 Methods

2.1 Literature search

A comprehensive search was performed using two major English electronic databases (Embase and Medline) and a combination of search terms in the title, abstract, keyword, subject word, or study citation. The detailed process of literature search, including the specific search terms and inclusion and exclusion criteria, is presented in Fig. 1.

2.2 Inclusion criteria

We selected studies that (1) were published before April 2019; (2) involved childhood cancer survivors (patients diagnosed with cancer before the age of 19 years who had completed active treatment and received neurocognitive assessments); (3) applied performance-based cognitive assessments, or self-reported tools that focus specifically on assessing cognitive function; (4) were randomized controlled trials, non-randomized controlled trials, cross-sectional studies, or prospective/retrospective observational clinical studies; (5) were published in English; and (6) involved childhood cancer survivors in countries or regions in East Asia (Mainland China including Hong Kong and Macau, Taiwan, Mongolia, Japan, South Korea) or Southeast Asia (Brunei, Myanmar, Cambodia, Indonesia, Laos, Malaysia, the Philippines, Singapore, Thailand, Timor-Leste, and Vietnam). We excluded countries from the Middle East, South Asia, and Central Asia because of economic, cultural, and social disparities [27–30].

2.3 Exclusion criteria

The following items were excluded: (1) reviews, meta-analysis papers, case reports, or commentaries; (2) *in vivo* or *in vitro* studies without human data; (3) conference abstracts or poster abstracts without full-text publication; and (4) studies of health outcomes that were conducted during the active treatment phase.

2.4 Data extraction

Two investigators (LP and PYY) reviewed the search results independently on three successive levels. (1) Initially, the article titles were screened to exclude studies that were unrelated to the aims of this review (title stage). (2) Next, the abstracts of the articles that passed the title stage were further reviewed (abstract stage). (3) In the final stage, the full texts of the remaining articles were reviewed to ensure that they fulfilled the inclusion or exclusion criteria (full-text stage). Subsequently, using a standardized methodology, the investigators (LP and PYY) independently summarized the author, publication year, region, sample size of the treatment and control groups (if any), sex, study design, cancer type, age at diagnosis, follow-up time, age at recruitment, classifications of treatment, outcome assessments, results, and risk factors described in the articles. The list of included studies and the summaries of data were then compared and standardized through discussions with a third investigator (YTC). The accuracy of the final extracted data was checked independently by another investigator (LSY).

The methodological quality of the included studies was assessed using the quality assessment tool for observational cohort and cross-sectional studies [31] which is widely applied in appraising the methodological quality of observational cohort studies and cross-sectional studies [32, 33]. The inter-rater reliability was calculated using Cohen's kappa statistic to ascertain the scoring agreement between the two investigators (LP and PYY) [30].

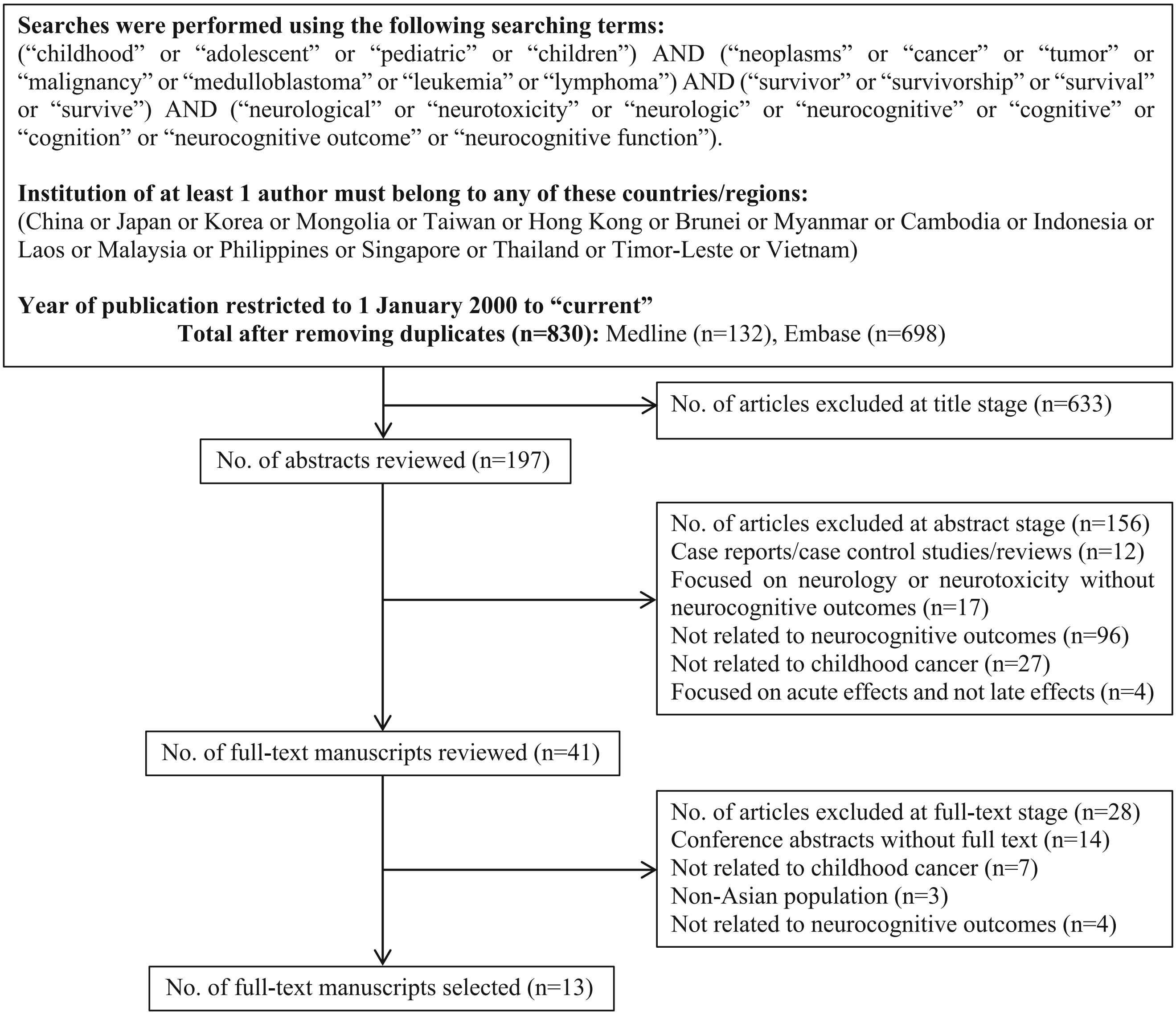

Fig. 1 Flowchart of literature search

3 Results

3.1 Study selection

The results of the literature search are presented in Fig. 1. A total of 830 titles were identified from the databases. After excluding 633 articles at the title stage, 197 abstracts were further examined. Finally, 41 full-text manuscripts were reviewed, from which, 13 studies were found to fulfill the inclusion criteria.

3.2 Population characteristics

The population characteristics of the 13 included studies are summarized in Table 1. A total of 2212 participants were represented by the included literature, comprising 894 childhood cancer survivors in the treatment arm and 1318 community or sibling controls. Among the survivors in the included studies, the male-to-female ratio was approximately 1.5:1. The percentage of male survivors was 60.1% ($n = 537$) [34–46]. Most of the included studies were conducted in developed countries including South Korea ($n = 4$, 30.8%) [37–40], Taiwan ($n = 3$, 23.1%) [35, 43, 45], Japan ($n = 3$, 23.1%) [41, 42, 44], and Hong Kong ($n = 2$, 15.4%) [36, 46]. Only one recent study was conducted in a developing country (Thailand) [34].

As shown in Table 1, all studies adopted an epidemiological study design, including cross-sectional studies ($n = 9$, 69.2%) and retrospective cohort studies ($n = 4$, 30.8%). Of the 13 studies, 8 had small-to-moderate sample sizes (20–100 participants), 4 had large sample sizes (100–250 participants), and 1 study had a cohort of 1185 participants. Over

Table 1 Population characteristics of the included studies ($n = 13$)

Author (year) (index)	Region	Sample size		Percentage of male	Study design	Cancer Type	Age at dx mean ± SD (range) in years	Follow-up time mean ± SD (range) in years	Age at recruitment mean ± SD (range) in years	Treatment			
		tx	**ctrl**							Chemo (%)	Rtx (%)	HSCT (%)	Surgery (%)
Ketsuwan (2019) [34]	Thailand	100	37	59.0%	Cross-sectional study	ALL (39.0%), EGCT (19.0%), soft tissue sarcoma (15.0%), neuroblastoma (12.5%)	4.4 ± 3.2	5.5 ± 2.4 post-tx	11.1 ± 2.8	NR	0	NR	NR
Chiou (2019) [35]	Taiwan	42	NA	61.9%	Cross-sectional study	ALL	4.8 (0.3–1-6.9)	8.4 (3–18.5) post-tx	17.8 (9–31.2)	NR	NR	NR	NR
Tso (2018) [36]	Hong Kong	25	NR	68.0%	Retrospective cohort study	Intracranial germ cell tumor: GCT (36.0%), NGGCT (64.0%)	13.3 (7.7–1-7.7)	6.4 (1.2–12.2) post-tx	NA	100.0%	100.0%	NA	28.0%
Kim (2018) [37]	South Korea	145	NA	60.7%	Cross-sectional study	Hematological (58%), solid or soft tissue (34.2%), CNS (6.9%) tumors	7.4 ± 4.1 (0–16)	8.0 ± 3.9 (0–16.1) post-dx	15.33 ± 1.7 (13–19)	95.2%	32.4%	16.6%	41.2%
Oh (2017) [38]	South Korea	51	NA	70.6%	Retrospective cohort study	Brain tumor: embryonal (49.0%), glial (3.9%), germ cell (47.1%) tumor	10.1	13.5 (weeks) post--dx	NR	100.0%	100.0%	NA	100.0%
Yoo (2016) [39]	South Korea	58	NA	62.1%	Cross-sectional study	Medulloblastoma	8.0 (1–22)	< 3 years (22.4%); > 10 years (19.0%) post-dx	13.7 (6–26)	46.6%	81.0%	NA	NR
Kim (2015) [40]	South Korea	42	42	59.5%	Cross-sectional study	ALL	3.8 ± 2.3	6.6 ± 1.3 post-dx	10.5 ± 2.4	100.0%	42.9%	0%	0%
Sato (2014) [41]	Japan	104	NA	74.0%	Cross-sectional study	Germinoma (42.3%), other GCT (10.6%), medulloblastoma/PNET (10.6%), glioma (24.0%), others (12.5%)	11.4	7.8 post-tx	21.0	71.2%	82.7%	NA	88.5%
Odagiri (2014) [42]	Japan	24	NA	66.7%	Retrospective cohort study	Medulloblastoma (66.7%), sPNET (16.7%), AT/RT (12.5%), pineoblastoma (4.2%)	6.0 ± 4.3 (0.3–1-6)	5.4 ± 2.6 (1.6–9.8) post-dx	11.5 ± 5.6 (2.8–22.6)	100.0%	100.0%	62.5%	100.0%
Liang (2013) [43]	Taiwan	56	NA	76.8%	Retrospective cohort study	Intracranial germ cell tumor: germinoma (62.5%), mature teratoma (1.8%), NG-MGCT (35.7%)	11.9 (3.2–1-9.9)	6.9 (1.7–17.9)	17.7 (8.9–29.1)	48.2%	94.6%	NA	69.6%
Ishida (2010) [44]	Japan	185	1000	41.6%	Cross-sectional study	Hematological (69.2%), brain (5.4%), bone or soft tissue sarcoma (9.7%), other solid tumor (15.7%)	8.3	1–4 years (2.7%); 5–9 years (27.0%); 10–14 years (30.8%); ≥ 15 years (39.5%) post-tx	23.1	NR	61.1%	24.9%	37.8%
Chiou (2009) [45]	Taiwan	32	184	53.1%	Cross-sectional study	ALL	4.4 ± 2.2 (0.8–1-0.8)	8.7 ± 2.3 (5.3–13.9) post-dx; 7.5 ± 2.4 (3.0–13.2) post-tx	13.2 ± 2.5 (8.9–18.9)	100.0%	18.8%	0%	NA

Table 1 (continued)

Author (year) (index)	Region	Sample size		Percentage of male	Study design	Cancer Type	Age at dx mean ± SD (range) in years	Follow-up time mean ± SD (range) in years	Age at recruitment mean ± SD (range) in years	Treatment			
		tx	ctrl							Chemo (%)	Rtx (%)	HSCT (%)	Surgery (%)
Khong (2006) [46]	Hong Kong	30	55	66.7%	Cross-sectional study	Medulloblastoma (40.0%), ALL (60.0%)	7.4	5.7	13.1 (6.0–22.1)	100.0%	70.0%	0%	40.0%

Studies are arranged in chronological order of publication

tx, treatment group; *ctrl*, control group; *dx*, diagnosis; *ALL*, acute lymphoblastic leukemia; *AT/RT*, atypical teratoid/rhabdoid tumor; *Chemo*, chemotherapy; *CNS*, central nervous system; *EGCT*, extracranial germ cell tumor; *GCT*, germ cell tumor; *HSCT*, hematopoietic stem cell transplantation; *NA*, not available; *NGGCT*, non-germinomatous germ cell tumor; *NG-MGCT*, non-germinomatous malignant germ cell tumor; *NR*, not reported; *PNET*, primitive neuroectodermal tumor; *Rtx*, radiotherapy; *SD*, standard deviation; *sPNET*, supratentorial primitive neuroectodermal tumor

half of the studies focused on either survivors of childhood CNS tumors (e.g., medulloblastoma and intracranial germ cell tumor; $n = 10$, 76.9%) or hematological malignancies (e.g., acute lymphoblastic leukemia (ALL), $n = 7$, 53.8%). The remaining studies involved a heterogeneous cancer diagnoses ($n = 3$, 23.1%). The common treatment modalities were chemotherapy ($n = 10$, 76.9%), CRT ($n = 9$, 69.2%), hematopoietic stem cell transplantation ($n = 3$, 23.1%), and surgery ($n = 8$, 61.5%). Most studies recorded the neurocognitive outcomes in patients during the early stage of survivorship (5 years post-treatment).

3.3 Reporting quality assessment of the studies

The qualities of all included studies were rated as either "moderate" ($n = 7$, 53.8%) or "high" ($n = 6$, 46.2%) (Table 2). Overall, owing to the strict inclusion criteria adopted in this review, all included studies fulfilled the requirements of a robust epidemiological study, such as stating an explicit study objective, including a well-defined study population, providing a detailed definition of the measurement of both exposure and outcome, having sufficient timeframe to observe an effect, and incorporating appropriate adjustment for confounding factors. However, potential bias due to loss to follow-up may exist as most of the studies did not document the participation rate.

3.4 Neurocognitive outcomes of the studies

The neurocognitive assessments, prevalence, and risk factors associated with neurocognitive impairments are reported in Table 3. Overall, the studies used a variety of performance-based neurocognitive tests to examine the cognitive domains of intelligence, attention, executive function, memory, motor function, and manual dexterity of the participants.

Most of the studies assessed intelligence using age-adjusted tools of Wechsler Intelligence Scale for Children or Wechsler Adult Intelligence Scale ($n = 10$, 76.9%). Some studies also included non-performance-based tests to assess self-reported cognitive function, quality of life, behavior, and psychosocial stress. One study included magnetic resonance imaging to examine the association between neurotoxicity and neurocognitive function by assessing the loss of white matter fractional anisotropy [46]. Nearly half of the studies reported mild-to-moderate impairment in 10.0–42.8% of survivors, particularly in the intelligence domain [35, 36, 39, 42, 45, 46]. We found that childhood cancer survivors had lower overall intelligence quotient scores compared with healthy controls [34, 40]. Two studies reported mild-to-moderate impairments in attention, concentration, executive functions, memory, and intelligence in childhood cancer survivors [39, 40]. Moreover, patients who were diagnosed at a younger age or had undergone CRT tended to perform poorly [39, 40].

Table 2 Critical appraisal within source of evidence

Author	Clear objective	Population defined	Participation rate ≥ 50%	Include/ exclude list	Sample size	Exposures prior to outcomes	Sufficient timeframe	Different levels of exposure	Exposures well-defined	Outcome measures defined	Loss to follow-up ≤ 20%	Confounding factors	Overall quality (total score)
Ketsuwan (2019) [34]	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	NA	Y	High (10)
Chiou (2019) [35]	Y	Y	Y	Y	N	Y	Y	NA	Y	Y	NA	N	Moderate (8)
Tso (2018) [36]	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Moderate (8)
Kim (2018) [37]	Y	Y	Y	Y	N	Y	N	N	Y	Y	NA	Y	Moderate (8)
Oh (2017) [38]	Y	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	High (11)
Yoo (2016) [39]	Y	Y	NR	Y	N	Y	N	NA	Y	Y	NA	Y	Moderate (7)
Kim (2015) [40]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	NA	Y	High (10)
Sato (2014) [41]	Y	Y	Y	Y	N	Y	Y	N	Y	Y	NA	Y	High (9)
Odagiri (2014) [42]	Y	Y	NR	N	N	Y	Y	Y	Y	Y	N	Y	Moderate (8)
Liang (2013) [43]	Y	Y	NR	N	N	Y	Y	Y	Y	Y	NA	Y	Moderate (8)
Ishida (2010) [44]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	NA	Y	High (10)
Chiou (2010) [45]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	NA	Y	High (10)
Khong (2006) [46]	Y	Y	NR	N	N	Y	Y	Y	Y	Y	NA	Y	Moderate (8)

Y, yes; *N*, no; *NA*, not applicable; *NR*, not reported

Assessment criterion regarding whether exposures are assessed over once is removed, as they are not applicable for most patients who received treatment exposure at a single time point; assessment criterion regarding blinding is also removed as it is not applicable

Overall quality (total score 12): high (score 9–12); moderate (score 5–8); low (score 4 or below)

Table 3 Outcome assessments and major findings of the included studies ($n = 13$)

Author (Year)	Region	Outcome assessment tools		Outcomes (prevalence or comparison with control group)	Factors associated with neurocognitive impairment
		Cognitive assessment tools	Other outcome measures		
Ketsuwan (2019) [34]	Thailand	• Intelligence: WISC-III	NA	• Lower IQ scores in survivors than controls, including subscales of information, similarities, block design, object assembly subsets	• Low socioeconomic status • Low level of parents' education
Chiou (2019) [35]	Taiwan	• Intelligence: WISC-IV • Attention: CPT II • Executive function: WSCT	• Behavior: CBCL • ADHD diagnosis: ASRS	• Chronic mental condition (14.3%); • FSIQ 91.7 ± 13.8 (66–112); inattention (10%); impulsivity (20%); impaired in executive functions (42.8%) • Chronic physical conditions (40.5%) • Obvious attention problem in daily life (42%), with 3 subjects diagnosed with ADHD. For adult subjects, highly probable ADHD (61.9%); for nonadult subjects, marked attention problems (27.8%) • No difference in cognitive outcomes between standard risk vs high/very high-risk patients	NR
Tso (2018) [36]	Hong Kong	• Intelligence: WISC-IV/WAIS-III • Manual dexterity: motoric pegboard test	• Performance: LPP/KPS • QoL: PedsQL 4.0	• Borderline IQ or worse (24.0%) • KPS scores ≤ 70 (16%) • Lower physical scores in survivors than controls	• Longer follow-up time
Kim (2018) [37]	South Korea	• Cognitive function: subscale of MMQL	• Depression: BDI • Peer exclusion and victimization: MHDCCA	• Depression (6.4%) • Peer-exclusion experience (49.7%) • More peer exclusion-victimization and lower cognitive functioning were associated with depressive symptoms	• Depressive symptoms
Oh (2017) [38]	South Korea	• Intelligence: WISC-III, IV	• Attention: CBCL-APS • Psychosocial outcomes: K-PRC	• Survivors who had attention problems reported more depressive symptoms, delinquency, hyperactivity, and family relationship problems	• Younger age at diagnosis
Yoo (2016) [39]	South Korea	• Intelligence: KWISC-III/KWAIS • Attention: digit span forward, CTT 1 • Memory: RKMT, KAVLT, KCFT • Executive function: COWA, digit span backward, CTT2 • Motor function: grooved pegboard, grip strength test	• QoL: Peds-FACT-BrS	• Overall poorer IQ and impaired memory function compared with reference norms • FSIQ, VIQ, PIQ below average (19.0%, 12.1%, 29.3% respectively) • Mean MQ: 39.7% below 1SD, 8.6% below 2SD • Mild-to-moderate deficits in processing speed, attention, executive function	• Younger age at diagnosis • Earlier exposure to cranial radiation and chemotherapy
Kim (2015) [40]	South Korea	• Intelligence: KEDI-WISC • Executive function: CTT, STROOP • Attention: ADS	NA	• Lower FSIQ, PIQ, VIQ of irradiation group than non-irradiation and control group • Poor attention, concentration, executive functions in survivors	• Cranial irradiation • Male sex • Younger age at diagnosis
Sato (2014) [41]	Japan	• Cognitive function: subscales of PedsQL BTM/QLQ C30	• QoL: QLQ C30, QLQ CM20/ PedsQL GCS, BTM, CM	• Higher impairment related to diminished HRQOL • Motor and cognitive dysfunction related to ocular/visual impairment in survivors aged 12 to 17	• Ocular/visual impairment • Diminished HRQOL
Odagiri (2014) [42]	Japan	• Intelligence: WISC III, TBIS, KSPD 2001	NA	• The differences between initial and latest IQ tests were significant, ranging from 5 to − 39 (median, − 10) • The latest FSIQ ranging from 59 to 128 (median, 86) • Two survivors presented severe mental retardation with FSIQ < 70	• Craniospinal irradiation dosage and age at starting irradiation did not impact FSIQ scores
	Taiwan	• Intelligence: WISC-IV/WAIS-III		• Lower FSIQ for basal ganglia tumor than pineal and suprasellar regions	• Extensive irradiation field

Table 3 (continued)

Author (Year)	Region	Outcome assessment tools		Outcomes (prevalence or comparison with control group)	Factors associated with neurocognitive impairment
		Cognitive assessment tools	Other outcome measures		
Liang (2013) [43]		• Memory: digit/spatial span test of the WMS-III, word list of WMS-III, recognition trial, RCFT • Attention: vigilance task of GDS • Executive function: WCST	• Behavior: ABAS-II/CHQ-P-F50	• Group differences in IQ, verbal and visual memory, QoL, adaptive skills, psychosocial domains • Better cognitive outcomes for patient treated with whole-ventricular irradiation	• High irradiation dosage
Ishida (2010) [44]	Japan	• Cognitive function: subscale of CTCAEv3	• Other health outcomes: CTCAEv3 • QoL: NR	NR	• Skull and spinal irradiation
Chiou (2010) [45]	Taiwan	• Intelligence: WISC-III/WAIS-III • Cognitive health: Mindstream® assessment battery	• QoL: CHQ-PF50	• HRQL of survivors is lower than control • Impaired IQ (15.6%) • Impaired in cognitive domains (27.8%)	NR
Khong (2006) [46]	Hong Kong	• Intelligence: HK-WISC/WAIS-R	• Neuroimaging: MRI	• Medulloblastoma survivors have lowest cognitive outcomes, followed by ALL survivors with irradiation and ALL survivors without irradiation. • FSIQ, VIQ, PIQ below average (16.7%, 10.0%, 20.0%)	• Change in fractional anisotropy

Studies are arranged in chronological order of publication

ABAS-II, the Chinese adaptive behavior assessment system–second edition; *ADHD*, attention deficit/hyperactivity disorder; *ADS*, attention deficit hyperactivity disorder diagnostic system; *ALL*, acute lymphoblastic leukemia; *ASRS*, adult ADHD self-report scale; *BCM 20*, brain cancer module 20; *BDI*, Beck depression inventory; *BTM*, brain tumor module; *CBCL*, child behavior checklist; *CBCL-APS*, child behavior checklist-attention problem scale; *CHQ-PF50*, child health questionnaire 50-item parent form; *CISQ*, cancer institute's standardized questionnaire; *CNS*, central nervous system; *COWA*, controlled oral word association; *CPT II*, Conners' continuous performance test II; *CTCAEv3*, common terminology criteria for adverse events, version 3; *CTT 1*, color trail making test 1; *CTT2*, color trail making test; *Dx*, diagnosis; *FSIQ*, full scale intelligence quotient; *GCS*, generic core scales; *GCT*, germ cell tumor; *GDS*, Gordon diagnostic system; *HK-WISC*, Hong Kong Wechsler intelligence scale for children; *HRQL/HRQOL*, health-related quality of life; *IQ*, intelligence quotient; *KAVLT*, K-auditory verbal learning test; *KCFT*, K-complex figure test; *KEDI-WISC*, Korean Educational Development Institute-Wechsler intelligence scale for children; *K-PRC*, Korean personality rating scale for children; *KPS*, Karnofsky performance scale; *KSPD 2001*, Kyoto scale of psychological development 2001; *KWAIS*, Korean Wechsler adult intelligence scale; *KWISC-III*, Korean Wechsler intelligence scale for children–III; *LPP*, Lansky play-performance scale; *MHDCCA*, mental health diagnostic checklist for children and adolescent; *MISIC*, Malins intelligence scale for Indian children; *MMQL*, Minneapolis-Manchester quality of life; *MQ*, memory quotient; *MRI*, magnetic resonance imaging; *NA*, not available; *NGGCT*, non-germinomatous germ cell tumor; *NG-MGCT*, non-germinomatous malignant germ cell tumor; *NR*, not reported; *Peds-FACT-BrS*, pediatric functional assessment of cancer therapy-brain tumor survivors; *PedsQL*, pediatric quality of life inventory; *PIQ*, performance intelligence quotient; *QLQ C30*, quality of life questionnaire core questionnaire 30; *QLQ CM20*, quality of life questionnaire brain cancer module 20; *QoL*, quality of life; *RCFT*, Rey complex figure test; *RKMT*, Rey-Kim memory test; *SD*, standard deviation; *STROOP*, stroop color and word test: children's version; *TBIS*, Tanaka-Binet intelligence scale; *VIQ*, verbal intelligence quotient; *WAIS-III*, Wechsler adult intelligence scale–III; *WAIS-R*, Wechsler adult intelligence scale-revised; *WCST*, Wisconsin card sorting test; *WISC-IV*, Wechsler intelligence scale for children–IV; *WMS-III*, Wechsler memory scale-third edition

Childhood medulloblastoma survivors exhibited poorer cognitive outcomes compared with childhood ALL survivors, which suggested that the effects on cognitive performance may vary across different cancer types [46]. Among the intracranial germ cell tumor survivors, those with tumors in the basal ganglia site had poorer cognitive performance than those with tumors in the pineal or suprasellar sites [43]. We also found that an extensive irradiation field and a high irradiation dosage contributed to worse cognitive outcomes such as intellectual malfunction, executive malfunction, and memory problems [43]. Follow-up time, age at diagnosis, sex, early exposure to radiation, and chemotherapy were also found to be risk factors for poor neurocognitive outcomes [34, 36, 38–40, 43, 44, 46].

Survivors who reported depressive symptoms, family stress, and psychosocial problems exhibited more severe neurocognitive impairment [37, 38]. In one study, severe depression was found to be associated with poorer cognitive functioning and peer exclusion victimization [37]. Lastly, psychosocial symptoms such as anxiety, depression, delinquency, and poor family and emotional relationships tended to manifest more often in childhood cancer survivors with attention problems [38].

4 Discussion

To our knowledge, this is the first review that systematically analyzed the neurocognitive outcomes of Asian childhood cancer survivors. Our review highlighted the scarcity of high-quality studies investigating the neurocognitive outcomes in childhood cancer survivors in Asian countries. Nearly all studies reviewed here were conducted in high-income regions or countries with high childhood cancer survival rates and excellent survivorship care. We did not identify any similar studies reported from Mainland China or other developing countries in Southeast Asia. These countries typically have underdeveloped cancer survivorship programs and are also more likely to prioritize resources to other life-threatening problems such as secondary malignancy and cardiovascular complications. They may also lack certified neuropsychologists and developmental psychologists. Our review demonstrated disparities in the cognitive research programs for childhood cancer survivors between different Asian countries and regions. Given that educational attainment and academic achievement are highly regarded in many Asian societies, more studies focusing on neurocognitive outcomes in childhood cancer patients should be conducted in the future.

In almost half of the included studies, 10–43% of the patients who underwent chemotherapy, radiotherapy, or a combination thereof exhibited mild-to-moderate impairment in the intelligence domain. However, only 3–28% of such childhood cancer survivors exhibited similar impairments in the West [47, 48]. In a large-scale study in the USA, the intelligence impairment rate in the survivors with heterogeneous cancer diagnoses was reported to be 13% [49]. Thus, our findings suggested that childhood cancer survivors in Asia are more likely to develop intelligence impairment compared with childhood cancer survivors in the West, likely due to differences in the susceptibility and pathogenesis of cancer- and treatment-related neurocognitive dysfunctions between the two populations.

Thus, we postulate that the variability in neurocognitive outcomes in childhood cancer survivors between Western and Asian populations is determined by a combination of intrinsic and extrinsic factors (Fig. 2), which may include ethnic and culturally relevant risk factors. The following section discusses these risk factors:

4.1 Direct neurotoxic effects of treatment

Consistent with previous findings [64], we identified an association between high treatment intensity and neurocognitive dysfunction [43]. High doses of CRT or chemotherapy are correlated strongly with neurocognitive impairments [36, 39, 40]. Although the treatment protocols for childhood cancer adopted in most developed Asian countries or regions are similar to those in Western countries, the generalized use of contemporary treatment is still rare in some regions in Asia. CRT has largely been replaced by contemporary risk-adapted chemotherapy-only regimens to reduce the risk of neurocognitive impairment and neurotoxicity in childhood leukemia survivors in developed countries [65]. Most of the Asian countries recently also adopt similar strategy of reducing the use of CRT in their leukemia treatment protcols, hence the long-term neurotoxic late effects in these survivors require further studies.

Furthermore, chemotherapy-only regimens also promote the development of neurocognitive impairment in childhood cancer survivors in a dose-dependent manner [66, 67]. Thus, pharmacogenetic research that predicts chronic drug toxicities is crucial to help improve treatment outcomes [68]. For example, Malaysian adults with *MTHFR C677T* and *ABCB1 C3435T* polymorphisms typically exhibit elevated plasma methotrexate accumulation compared with the general population [69]. Therefore, high-dose methotrexate treatment may lead to poorer cognitive outcomes in this population [50, 51]. Future studies should evaluate the impact of genetic factors and plasma methotrexate–related neurotoxicity to improve our understanding of the variability in the long-term neurocognitive outcomes among cancer survivors of different ethnic backgrounds.

4.2 Indirect effects of cancer and treatment

Aging survivors of childhood cancer develop post-treatment chronic health conditions at higher rates compared with age-matched sibling controls and the general population [70, 71].

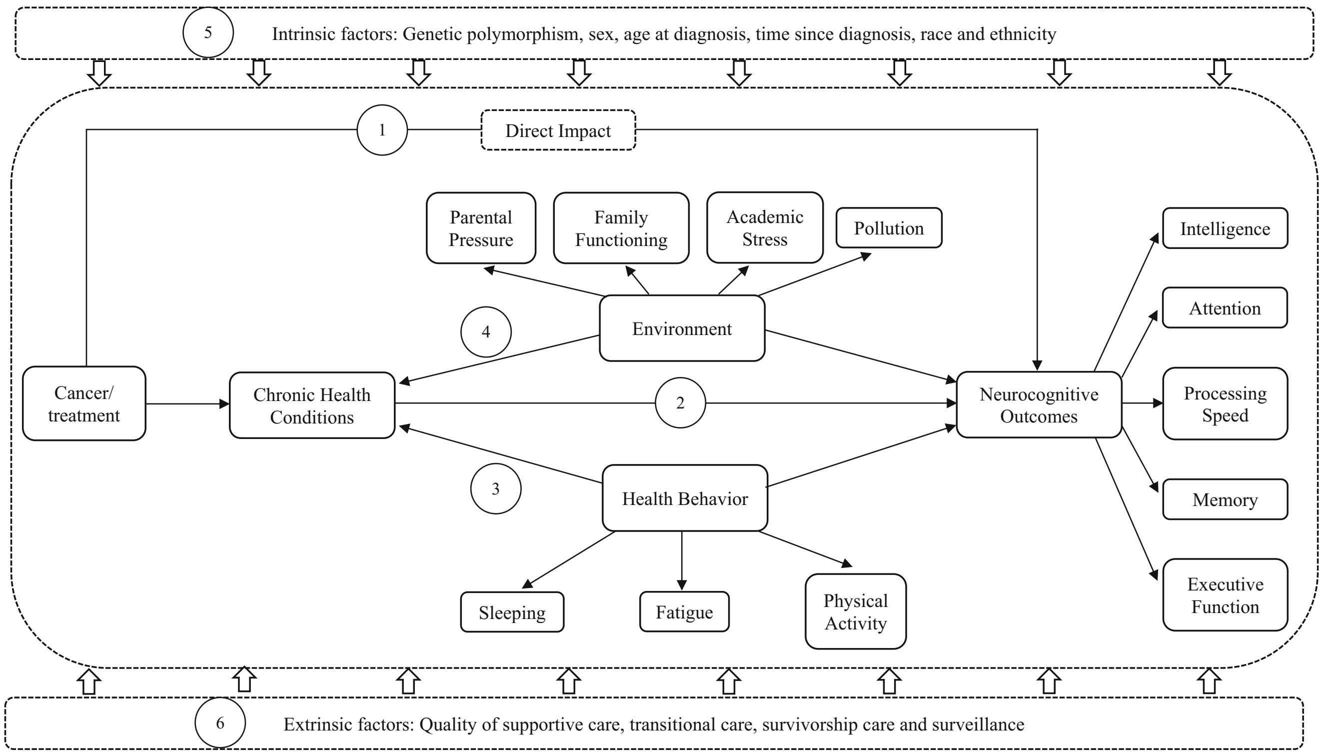

Fig. 2 Model of direct and indirect impact of cancer and treatment on neurocognitive outcomes in long-term childhood cancer survivors. 1 Direct effects of cancer and treatment. We hypothesize that cancer and treatment can have direct neurotoxic effects on the brain, leading to long-term neurocognitive outcomes. High doses of CRT or chemotherapy are associated strongly with neurocognitive impairments [36, 39, 40]. For example, it was demonstrated that high-dose methotrexate treatment contributed to poorer cognitive outcomes [50, 51]. 2 Indirect neurotoxic effect through chronic conditions. Neurocognitive impairment can be mediated by treatment-related chronic conditions such as cardiovascular, pulmonary, and endocrine conditions [52, 53]. For example, anthracyclines is known to cause cardiovascular complications, and cardiopulmonary morbidities were associated with poor memory and task efficiency in childhood cancer survivors [54]. 3 Influence of health behavior. Health behavioral factors including physical inactivity, smoking, alcoholism, sleep problems, and fatigue can contribute to neurocognitive dysfunction [55–58]. Sleep disturbance and fatigue are associated with poorer cognitive flexibility and fluency in childhood cancer survivors [59]. Physical inactivity and sedentary lifestyle are significant risk factors for the poor sleep quality and fatigue, which may also have an indirect effect on cognitive problems [58, 60]. 4 Influence of the environment. We speculate that the environmental factors including contamination, academic stress, and family functioning could have an impact on the development of long-term cognitive problems. Early childhood adversity was associated with deficits in memory and executive function [55]. Air pollution from industrialization and second-hand smoke and water pollution such as lead and mercury contamination can significantly impair brain function in both children and adults [61]. 5 Intrinsic factors. From active treatment to long-term survivorship, intrinsic factors could have a lifelong effect on brain development, resulting in neurocognitive dysfunction. These factors comprise genetic polymorphism, sex, age at diagnosis, time since diagnosis, race, and ethnicity. Younger age at diagnosis has been reported to be associated with the poor neurocognitive outcomes [38–40]. Female survivors of CNS tumor are at higher risk of neurocognitive impairment than male survivors [62]. 6 Extrinsic factors. The quality of supportive care during active treatment may minimize acute adverse effects, which may subsequently reduce symptom burden and long-term toxicities on the organ systems [63]. Compensatory strategies in the form of health behavioral and psychological interventions could help childhood cancer survivors prevent or minimize the severity of neurocognitive disorders [48]

These chronic morbidities include cardiovascular, pulmonary, endocrine, and cerebrovascular complications [72, 73]. Previous population-based studies have suggested that the clinical manifestations of these chronic morbidities are associated with cognitive impairment and psychosocial difficulties in childhood cancer survivors [52, 53]. Another study from the Childhood Cancer Survivor Study reported an association between cardiopulmonary conditions and poor memory and task efficiency in childhood cancer survivors in the USA [54]. Notably, the prevalence and risk factors for late cardiopulmonary effects in the Asian population are different from those in the Western population. For example, obesity is less common in Asian survivors than in Western survivors [30]. Our group recently reviewed the clinical studies on the late effects in Asian childhood cancer survivors, which indicated potential differences in the prevalence of late effects between Asian and non-Asian populations [30]. Future work should investigate the impact of chronic health status on the neurocognitive function in aging survivors and address the modifiable risk factors during the early phase of survivorship.

Studies have also shown that systemic inflammatory dysregulation is associated with poor cognitive outcomes. Indeed, high plasma levels of IL-6, IL-8, IL-1β, TNF-α, and MCP-1 negatively predict attention and memory performance in adolescent survivors of childhood cancer [74–76]. One study demonstrated that elevated uric acid levels during adolescence were correlated with cardiovascular morbidity during adulthood and poorer neurocognitive outcomes in childhood ALL survivors [77]. The effects of inflammation and vascular injury on the development of chronic morbidities may also differ between the Western and Asian populations due to habitual differences such as in physical activity and dietary pattern. This may in turn contribute to the differences in the etiologies of neurocognitive impairment in Asian survivors.

4.3 Health behavior and lifestyle

In the general population, lifestyle factors including physical inactivity, smoking, alcoholism, sleep problems, childhood adversity, and stress can contribute to the development of neurocognitive impairment [55–58]. Sleep disturbance and fatigue are associated with poorer cognitive flexibility and fluency in adolescent survivors of childhood ALL [59]. Physical inactivity is a significant risk factor for poor sleeping patterns and fatigue and has been shown to have an indirect effect on cognitive disorders in both the general population and cancer survivors [58, 60]. Previous studies have suggested that exercise intensity and frequency differ between Asian and Western populations. Specifically, compared with Western populations, Asians tend to engage less in moderate-to-vigorous intensity activities but are less sedentary [60]. Tobacco use and alcohol consumption are known to be associated with cognitive dysfunction through the indirect effects of cardiovascular and cerebrovascular injuries [78–80]. Smoking is another strong risk factor for cardiovascular diseases, but its prevalence varies among Asian countries. According to the World Health Organization, the age-standardized prevalence of tobacco use is considerably higher in Mainland China (25.2%), Japan (22.5%), and Korea (23.6%) compared with that in other Asian countries such as India (11.3%) and Singapore (16.8%) [81]. Future research should continue to explore the relationships between ethnicity and lifestyle behaviors and their impacts on the neurodevelopment of childhood cancer survivors.

Stress, mental health, and psychological distress may differ between the ethnic groups. Consistent with this idea, a previous study found that many quality-of-life outcomes were different between Hispanic black, non-Hispanic black, and non-Hispanic white childhood cancer survivors, but neurocognitive outcomes did not differ [82]. For adolescents in developed Asian countries, the constant pressure to achieve academic excellence may exacerbate symptoms of stress and mental health problems [83, 84]. In contrast, the definitions of achievement in life are more diverse in Western societies. The differences in neurocognitive and psychological functioning between different ethnic groups emphasize the need to tailor the behavioral and psychological targets of interventions in local and regional programs in areas with multi-ethnic communities.

4.4 Living environment

Over the past decade, the unprecedented population growth and economic development have contributed to many environmental problems in Asia. Indeed, environmental characteristics, such as contamination, noise pollution, overcrowding, and housing problems, are known to influence neurodevelopment in children [85–89]. This is especially relevant for low-income families in certain regions of Asia where poverty is frequently associated with multiple environmental risks. Lead and mercury contamination in water can significantly impair brain functioning in both children and adults and is a pressing public health issue in Mainland China and India [61]. Moreover, small living spaces and old housing properties are also correlated with increased psychological distress [90]. There are limited studies that evaluate the association between the living environment and cognitive function in childhood cancer survivors. Although the adverse impact of individual environmental risk factors on the cognitive development of children is not entirely understood, childhood cancer survivors who are already at a higher risk of developing neurocognitive impairment (due to primary treatment exposures) may be more vulnerable to the effects of a poor living environment.

5 Study limitations

Owing to our stringent selection criteria, this study is limited by the small sample size and restricted geographical coverage. Secondly, our cohort of the included studies lacks any large-scale epidemiological studies with prospective follow-up procedures and comprehensive surveillance data on cognitive outcomes. Most of the reviewed studies were conducted in a single-centered clinical venue ($n = 8$, 61.5%), which may have led to misrepresentation of the prevalence because of the risk factors specific to that patient catchment area. Moreover, the outcome assessments varied among the included studies, especially for the measures of memory, attention, and executive and motor functions, which made the systematic analysis and summarizing of the neurocognitive outcomes difficult. Nevertheless, our restriction to studies that used performance-based measures or self-reported cognitive-specific measures to assess neurocognitive outcomes ensured the robustness of our review, as the quality appraisal revealed that all included studies had moderate-to-high methodological quality.

6 Conclusion

In this review, we systematically summarized the neurocognitive outcomes in Asian childhood cancer survivors and discussed the discrepancies in the prevalence of neurocognitive impairment between the Western and Asian populations. We speculate that the ethnic and genetic variations in drug responses and susceptibility to adverse chronic toxicities may have contributed to the differences in the prevalence, severity, and presentation of neurocognitive impairment between these two populations. Future studies should evaluate the contribution of environmental characteristics and lifestyle behaviors to neurodevelopment in Asian cancer survivors. This may aid the development of culturally relevant preventive and rehabilitative interventions (e.g., early screening of treatment-related chronic diseases) and identify the potential modifiable risk factors to improve the clinical and psychosocial outcomes of the patients (e.g., providing social support to improve the family environment).

We anticipate that the number of children with access to cancer treatment will drastically increase in Asia, which will also contribute to an increase in the number of cancer survivors over the next few years. To better understand the effects of culturally relevant and region-specific environmental risk factors on the post-treatment neurocognitive development in cancer survivors, a holistic approach that addresses the complex interactions between biological, physical, and psychosocial factors is needed. This will aid the development of effective intervention strategies to improve the functional and psychosocial outcomes of cancer survivors in Asian societies.

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Compliance with ethical standards

This study does not involve human or animals as subjects.

Conflict of interest The authors declare that they have no conflict of interest.

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