

Mental wellness and health-related quality of life of young adult survivors of childhood cancer in Singapore

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ABSTRACT

Introduction: Childhood cancer survivors (CCS) are at risk of experiencing psychological distress years after completing cancer treatments. We aimed to assess the prevalence and associated risk factors affecting psychological distress and health-related quality of life (HRQOL) among CCS in Singapore, and compare with their siblings without a history of or existing cancer as control.

Method: We recruited 143 young adult CCS aged ≥18 years attending survivorship clinics at KK Women's and Children's Hospital in Singapore who were in remission for ≥5 years and treatment-free for ≥2 years, and 57 siblings. CCS and siblings were matched at a 1:1 ratio based on sociodemographic factors yielding 46 pairs for comparison. Among CCS participants, 79 (55.2%) were male, 86 (60.1%) had leukaemia, 29 (20.3%) had solid tumours, 15 (10.5%) had lymphoma and 13 (9.1%) had brain tumours. All participants completed the Brief Symptom Inventory-18 (BSI-18) and Medical Outcomes Short Form-36 (MOS SF-36) questionnaires from August 2021 to July 2022.

Results: There were 35 (24.5%) CCS who reported psychological distress in the BSI-18 Global Severity Index. Five (3.5%) and 31 (21.7%) CCS reported low HRQOL in the physical and mental composite scores, respectively. Mean scores between CCS and their siblings were not statistically significant across all domains of the BSI-18 and MOS SF-36. Associated risk factors for psychological distress and low HRQOL among CCS were history of psychiatric illness after cancer diagnosis and mood affected by the COVID-19 pandemic.

Conclusion: CCS reported significant psychological distress and low HRQOL although they were not statistically different from their siblings. A holistic and risk factor-centric follow-up programme can aid early detection and mitigation of psychological late effects for CCS and their families.

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Keywords: cancer, depression, mental health, oncology, paediatrics, psychiatry, psychology, public health, quality of life

CLINICAL IMPACT

What is New

- To our knowledge, this cross-sectional study is the first to investigate the prevalence of psychological distress and health-related quality of life outcomes of childhood cancer survivors (CCS) in Singapore.
- Findings highlight that a significant proportion of CCS experience psychological distress.

Clinical Implications

- Cultural factors could be a cause for reluctance of CCS in Singapore to voice their stress, thus emphasising the need to use questionnaires as screening tools to monitor CCS' psychological wellness.
- This data can help in resource allocation for planning of survivorship programmes in Singapore.

INTRODUCTION

Advancements in technology and cancer treatments have improved childhood cancer survival rates, with up to 85% surviving 5 years or more.¹

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The Malaysia-Singapore Leukaemia Study Group reported an improvement in overall 5-year survival for the past 20 years in Singapore, from 69% to 91% for acute lymphoblastic leukaemia, which is the most common type of malignancy in childhood.²

Despite improvement in survival rate, adult childhood cancer survivors (CCS) often experience increased psychological distress and low health-related quality of life (HRQOL) due to the late effects of the disease and treatments. Significant physical disability and chronic illnesses arising from the complications of cancer, along with intensive treatment regimens like cranial irradiation, high-dose chemotherapy and surgical resection are associated with heightened psychological distress in CCS.³ These late effects encompass health issues arising at least 5 years post-remission and 2 years post-treatment, ranging from physical to psychological complications. The increased psychological distress, coupled with lower HRQOL, may also contribute to increased unemployment rates among CCS and increased reliance on social security assistance, posing an economic burden.⁴ This problem is especially important in Asia with half of the global cancer burden as of 2022.⁵

Early detection of psychological distress is paramount to improving mental wellness and HRQOL in CCS. Existing research on this topic suggests that cultures may influence the degree of psychological distress and HRQOL of CCS. Interestingly, previous studies in Asia do not see any statistical difference in psychological distress and HRQOL between CCS and their siblings as control, contrary to findings in Europe and America.^{6,7} We aimed to investigate the prevalence of psychological distress and low HRQOL among CCS in Singapore, as well as compare this with their siblings, given scarcity of such data in Southeast Asia. We also aimed to identify associated risk factors, which will help clinicians identify CCS with higher risk of having psychological distress. Additionally, since the study occurred during the COVID-19 pandemic, we wanted to know if the experience of going through a pandemic contributed to or affected the psychological distress and HRQOL of CCS.

METHOD

Study design

A cross-sectional, case-control study of young adult CCS attending survivorship clinics was conducted from August 2021 to July 2022 at KK Women's and Children's Hospital (KKH). KKH is the largest children's hospital in Singapore with more than 350 paediatric beds and manages the majority of childhood cancer patients in Singapore. The study

aimed to assess the prevalence of and associated risk factors for psychological distress and low HRQOL among CCS in Singapore, and compare these with their siblings who have no existing or history of cancer as control. The study was approved by the SingHealth Centralised Institutional Review Board (Reference number 2021/2404).

Study participants

CCS group

In the CCS group, 156 CCS were initially identified. Six CCS were excluded as they had neurocognitive impairment. Seven CCS did not give their consent. CCS with pre-existing psychiatric conditions before the diagnosis of cancer were excluded. A total of 143 (91.7%) CCS participants aged ≥ 18 years who have been in remission for at least 5 years and completed treatment for at least 2 years were recruited (Fig. 1).

Among the 143 recruited CCS participants, 86 (60.1%) patients had leukaemia, 29 (20.3%) had solid tumours, 15 (10.5%) had lymphoma and 13 (9.1%) had brain tumours. Seventeen (11.9%) patients had tumour recurrence and 2 (1.4%) patients had secondary neoplasm. There were 141 (98.6%) patients who had chemotherapy, 39 (27.3%) had radiotherapy, 60 (42.0%) had undergone surgery, and 12 (8.4%) had undergone bone marrow transplant. The mean age of diagnosis of the CCS was 7.7 (standard deviation [SD] 4.3) years and they completed treatment at the average age of 9.7 (SD 4.3) years. The average follow-up period of CCS was 16.8 (SD 6.0) years.

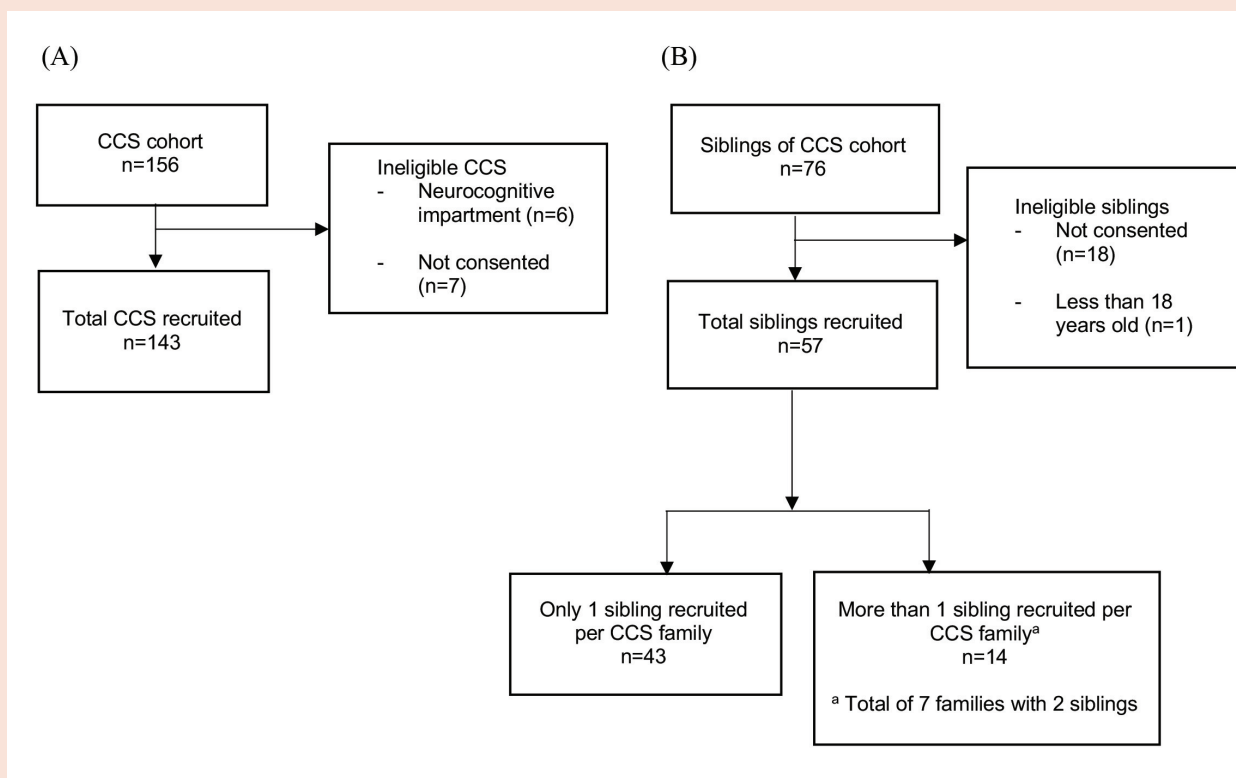
Control/siblings group

In the control group, 76 siblings of 69 CCS were initially identified and 57 (75.0%) were recruited (Fig. 1). The siblings had no history of childhood or existing cancers. Siblings were selected as the control arm in the study instead of the general population to account for potential confounders, such as different family upbringing and cultural influence.

Matching sociodemographic variables for comparison between CCS and siblings

Among the 143 CCS and 57 siblings recruited, 46 pairs were matched at a 1:1 ratio based on age, sex, ethnicity, educational level and household income. Compared to their siblings, a significantly higher proportion of CCS were employed/enrolled as students, single and had chronic illnesses. On average, CCS were also significantly younger than their siblings. There were 53 (37.1%) CCS and 25 (43.9%) siblings whose moods were affected by

Fig. 1. Flowchart inclusion of (A) childhood cancer survivors (CCS) and (B) their siblings.



the COVID-19 pandemic. The sociodemographic factors of CCS and their siblings are summarised in Table 1.

Individuals with significant neurological conditions or cognitive impairment rendering them unable to complete the questionnaires independently were also excluded. The participants had to be able to read, comprehend and write their answers on the questionnaires. This assessment was done by medically trained personnel in our research team.

Questionnaires

Psychological distress

Psychological distress was measured using the Brief Symptom Inventory-18 (BSI-18), an 18-item questionnaire with a main scale (Global Severity Index [GSI]) and 3 subscales (depression, anxiety and somatisation).⁸ Participants rated distress levels on a 5-point Likert scale for symptoms experienced in the last 7 days. Cumulative raw scores were converted to T scores (mean 50, SD 10). We used the BSI-18 manual published norms to calculate the T scores based on the US population, with a cut-off T score of ≥ 63 indicating significant psychological distress.⁸ We opted for the BSI-18 due to its reliability and validity in the CCS population.⁹

HRQOL

HRQOL was assessed using the Medical Outcomes Short Form-36 (MOS SF-36), a 36-item questionnaire with 8 domains representing various aspects of well-being. Domains include physical functioning, physical role limitations, bodily pain, general health perception, energy/vitality, social functioning, emotional role limitations and mental health. Each domain is measured by a scale from 0–100, with higher scores representing better HRQOL. We subsequently converted these scores into composite T scores to assess physical and mental dimensions in the form of physical health composite scores (PCS) and mental health composite scores (MCS) using the published norms.¹⁰ Participants with T scores of ≤ 40 (≤ 1 SD) in either PCS or MCS were classified as having poor HRQOL.¹¹ MOS SF-36 was shown to be reliable in screening for HRQOL in CCS populations, with reliability estimates ranging from 0.89–0.94 for PCS and 0.84–0.91 for MCS.^{7,10}

Study procedures

Both BSI-18 and MOS SF-36 forms were completed by CCS who have consented to participate during their visits to the survivorship clinic using paper forms, administered by a trained member of the study group who could also address any questions

Table 1. Sociodemographic factors of childhood cancer survivors (CCS) and their siblings (non-CCS).

Categories	CCS (n=143)	Non-CCS (n=57)	P value
Age, mean (SD), years	24.46 (5.01)	26.60 (5.78)	0.01
Male sex, no. (%)	79 (55.2)	24 (42.11)	0.09
Body mass index, no. (%)			
Underweight (<18.5 kg/m²)	17 (11.9)	11 (19.3)	0.08
Normal (18.5–22.9 kg/m²)	66 (46.1)	17 (29.8)	
Overweight/obese (≥23 kg/m²)	60 (42.0)	29 (50.9)	
Ethnicity, no. (%)			
Chinese	112 (78.3)	40 (70.18)	0.07
Malay	22 (15.4)	13 (21.70)	
Indian	9 (6.3)	2 (3.51)	
Others	0 (0)	2 (3.51)	
Highest education level, no. (%)			
Primary/secondary	14 (9.8)	5 (8.77)	0.19
Pre-university/polytechnic/diploma	72 (50.3)	25 (43.86)	
Undergraduate	45 (31.5)	16 (28.07)	
Masters/postgraduate	12 (8.4)	11 (19.39)	
Employed and/or enrolled as student, no. (%)	137 (95.8)	49 (85.96)	0.01
Household income, no. (%)			
<SGD 20,000	35 (24.5)	16 (28.07)	0.37
SGD 20,000–39,000	31 (21.7)	9 (15.79)	
SGD 40,000–59,000	28 (19.6)	7 (12.28)	
>SGD 60,000	49 (34.3)	25 (43.86)	
Marital status, married, no. (%)	14 (9.8)	13 (22.8)	0.02
Presence of chronic illness, no. (%)	100 (69.9)	6 (10.53)	<0.01
Types of late effects, no. (%)			
Cardiovascular disease	24 (16.8)	NA	0.37
Respiratory disease	6 (4.2)	NA	
Endocrine disease	64 (44.8)	NA	
Neurological disease	37 (25.9)	NA	
Psychiatric disease	11 (7.7)	NA	
Musculoskeletal and/or orthopaedic disease	13 (9.1)	NA	
Mood adversely affected by COVID-19, no. (%)	53 (37.1)	25 (43.9)	0.37

NA: not available; SD: standard deviation
P values in bold are statistically significant.

by the participants. The recruitment of participants was not done by any healthcare professionals who were directly involved in the care of patients to avoid undue influence. Siblings of CCS who met the study criteria were sent an email inviting their participation. The email contained the online version of the same forms with an explanation of the study's purpose and the nature of participation. If there was no reply via email, siblings were contacted via telephone once a week reminding them to respond. Siblings who did not pick up the telephone after 3 attempts or declined to be included in the study were excluded. If a CCS had more than 1 sibling, we invited all their siblings to complete the survey. There was no incentive provided for participating in this study.

Data collection and analysis

We initially identified potential risk factors affecting HRQOL and physiological distress from existing literature.³ These factors included demographic information, such as household income, education and employment status. The education and employment status might indirectly reflect the impact of late effects on social functioning of CCS. Additionally, medical details such as chronic illnesses that developed post-cancer diagnosis were extracted from case records using International Classification of Diseases, Ninth Edition codes. Self-reported psychological distress related to the COVID-19 pandemic was also assessed by asking participants an open-ended question.

Data analysis was conducted using IBM SPSS Statistics version 22 (IBM Corp, Armonk, NY, US). Continuous variables were presented as mean (SD), while categorical variables were expressed as proportions. Age and follow-up duration were compared using independent t-tests, while demographic differences were assessed using chi-square tests. A significance level of $P \leq 0.05$ was used. Associated risk factors ($P < 0.25$) in univariate analysis were identified for multivariate analysis via binary logistic regression, using a forward conditional method to evaluate independent contributions.

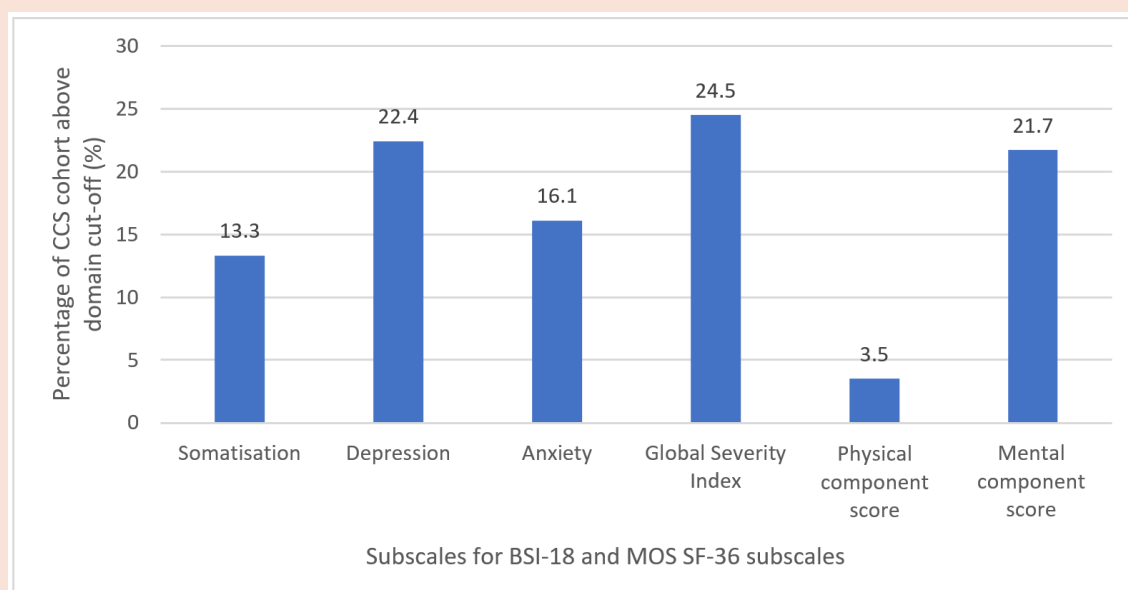
RESULTS

Prevalence of psychological distress/poor HRQOL in CCS and comparison with siblings

There were 19 (13.3%) CCS who reported significant elevation in BSI-18 somatisation subscale, 32 (22.4%) in the depression subscale, 23 (16.1%) in the anxiety subscale, and 35 (24.5%) in GSI. For HRQOL, 5 (3.5%) and 31 (21.7%) CCS reported poor HRQOL in PCS and MCS, respectively. Their scores are summarised in Fig. 2.

After matching each case-control based on age, sex, ethnicity, educational level and household income to account for possible confounders, there was a final total of 46 pairs (total 92 participants) for comparison between the CCS and control groups. There was no statistical difference in the

Fig. 2. Prevalence of psychological distress and poor health-related quality of life (HRQOL) in childhood cancer survivors (CCS).



BSI-18: Brief Symptom Inventory-18; MOS SF-36: Medical Outcomes Short Form-36

mean scores across all domains of the BSI-18 and MOS SF-36 between matched CCS and control as shown in Table 2. Statistical analysis of the remaining 11 siblings did not reveal any significant difference with the 46 siblings matched to the CCS.

Associated risk factors for psychological distress and low HRQOL in CCS

Among CCS participants, the associated risk factors for significant psychological distress were history of psychiatric illness (odds ratio [OR] 23.12, 95% confidence interval [CI] 4.38–121.98; $P < 0.01$) and mood being affected by the COVID-19 pandemic (OR 3.06, 95% CI 1.29–7.30; $P = 0.01$).

The associated risk factors for low HRQOL as quantified via MCS and PCS among CCS participants were a history of psychiatric illness (OR 33.07, 95% CI 5.62–194.52; $P < 0.01$) and mood being affected by the COVID-19 pandemic (OR 33.07, 95% CI 5.62–194.52; $P < 0.01$). The associated risk factors for significant psychological distress and low HRQOL are shown in Table 3.

DISCUSSION

This paper examined the psychological distress and HRQOL of CCS in Singapore over a follow-up period of almost 17 years, filling the gap in the literature of psychological late effects of CCS in Southeast Asia. We showed that the number of CCS with psychological distress and low HRQOL was significant, shown in 24.5% of CCS with high GSI in BSI-18 and 21.7% of CCS with low MCS in MOS SF-36. These results were comparable with previous American, European^{12–15} and Asian cohorts.^{6,16} Risk factors associated with poorer BSI-18, PCS and MCS included a diagnosis of psychiatric illness and mood affected by the COVID-19 pandemic. CCS with significant psychological distress were shown to score lower in HRQOL and had a higher likelihood of developing depression, anxiety and psychotic disorders.¹⁷ We advocate close monitoring and early referral to psychosocial services for CCS with psychiatric illness. Additionally, individuals whose moods were affected by the COVID-19 pandemic had lower scores on GSI, PCS and MCS, consistent with findings in a South African cohort.¹⁸ Strict lockdown measures in Singapore during specific periods were associated with increased rates of clinical depression, anxiety and stress disorders.¹⁹ A post-pandemic study is recommended to assess any changes in prevalence of psychological distress, low HRQOL and scores. Given the increasing evidence of COVID-19's long-term impact on mental health,²⁰ future studies should investigate its effects on the mental health

of CCS, particularly considering the impact of social distancing and isolation resulting from the pandemic.

We did not find any significant differences in the degree of psychological distress and HRQOL between CCS and their siblings across all domains of the BSI-18 and MOS SF-36. Existing literature presented varied results based on geographic regions regarding psychological distress assessed by BSI-18. An American cohort exhibited an increased risk of greater psychological distress across most BSI-18 domains among CCS compared to siblings,¹² whereas a Hong Kong cohort showed no significant differences.⁶ Similar contrasts in CCS and their siblings among Western and Asian cohorts were also reflected in HRQOL assessed using MOS SF-36.^{6,14,16} We hypothesise that cultural differences may contribute to these disparities. For instance, Chinese cultural norms emphasise virtues of self-control and perseverance, which may lead to diminished expressions of negative emotions explicitly.²¹ This cultural difference was illustrated in the US, where they found that Asian CCS were prone to suppress distressing emotions and pain related to cancer compared to non-Hispanic White CCS.^{22–24} This cultural context, coupled with recent findings suggesting variations in HRQOL across nationalities and culture, underscores the importance of local studies.²⁵

Another postulation that may explain differences in the extent of psychological distress among CCS cohorts is the type of coping mechanisms that CCS develop. Previous studies suggested that some CCS faced life's challenges with resilience and had a greater enthusiasm for life compared to the general population.²⁶ This possibly stemmed from the psychological resilience CCS cultivated while coping with the adversities during their childhood cancer treatment.²⁷ However, some subgroups of CCS developed maladaptive coping mechanisms, as seen in studies linking distress to negative thought suppression and low levels of optimism.^{28,29} In addition, Campbell et al. found that after the end of treatment, CCS who adopted a disengagement coping mechanism were found to be positively associated with subsequent behavioural problems.³⁰ Thus, additional studies examining both the qualitative and quantitative aspects between the types of coping mechanisms and severity of psychological distress are required to improve our understanding on the pathogenesis of psychological distress in CCS.

Specific to our cohort, the lower representation of CCS with brain and solid tumours (9.1% and 20.3%, respectively) compared to the national

Table 2. Comparison of the mean in the Brief Symptom Inventory-18 (BSI-18) T scores and Medical Outcomes Short Form-36 (MOS SF-36) scores between matched childhood cancer survivors (CCS) and siblings.

Subscales	CCS (SD) n=46	Siblings (SD) n=46	P value
BSI-18 T scores			
Somatisation	51.72 (8.86)	50.48 (10.12)	0.53
Depression	55.07 (10.52)	54.39 (9.69)	0.75
Anxiety	51.78 (10.30)	53.30 (9.77)	0.47
Global Severity Index	53.83 (10.60)	52.87 (10.93)	0.67
MOS SF-36 scores			
Physical functioning subscale score	92.39 (12.46)	85.87 (23.13)	0.10
Role physical subscale score	91.30 (24.28)	88.59 (23.40)	0.59
Bodily pain subscale score	86.36 (16.56)	81.69 (19.94)	0.23
General health subscale score	65.76 (16.90)	63.37 (13.95)	0.46
Vitality subscale score	56.63 (16.40)	51.41 (15.41)	0.12
Social functioning subscale score	81.79 (22.00)	79.89 (17.97)	0.65
Role emotional subscale score	86.23 (31.09)	74.64 (35.96)	0.10
Mental health	67.30 (15.44)	61.13 (17.30)	0.07
MOS SF-36 composite T scores			
Physical health summary component T score	53.76 (6.62)	52.70 (6.83)	0.46
Mental health summary component T score	46.34 (10.34)	43.30 (10.33)	0.16

SD: standard deviation

Table 3. Multivariate analysis of associated risk factors for mental distress and low health-related quality of life (HRQOL) in childhood cancer survivors.

Associated risk factors	Univariate odds ratio (95% CI); P value	Multivariate odds ratio (95% CI); P value
Global Severity Index ≥63		
Presence of chronic illness	2.00 (0.80–5.02); P=0.14	NA
History of psychiatric illness	18.25 (3.74–90.06); P<0.01	23.12 (4.38–121.98); P<0.01
History of endocrine illness	1.66 (0.77–3.58); P=0.19	NA
Family with cancer	2.00 (0.72–5.56); P=0.18	NA
Mood affected by COVID-19	3.03 (1.38–6.64); P<0.01	3.06 (1.29–7.30); P=0.01
Medical Outcomes Short Form-36 (physical and mental composite scores) ≤40		
Highest education	1.42 (0.83–2.42); P=0.20	NA
History of psychiatric illness	22.50 (4.55–111.34); P<0.01	33.07 (5.62–194.52); P<0.01
Mood affected by COVID-19	2.40 (1.11–5.19); P=0.03	3.18 (1.26–8.01); P=0.01

CI: confidence interval; NA: not available
P values in bold are statistically significant.

registry (14.1% and 42.5%, respectively) might have influenced reported outcomes.³¹ Brain and solid tumour survivors have generally exhibited poorer quality of life scores, increased psychological

distress and reduced social functioning compared to leukaemia survivors.^{14,32} This trend might have contributed towards the better-than-expected outcome scores of our CCS cohort.

Finally, we propose that another reason for the lack of statistical difference between the non-CCS and CCS groups could be due to the non-CCS group being equally affected by their sibling's childhood cancer diagnosis. In a large sample study by van Warmerdam et al.³³ the heightened risk of adverse mental health conditions among siblings of CCS only became evident around 15 years after diagnosis of childhood cancer. Notably, our cohort consisted of CCS and non-CCS with nearly 17 years of follow-up post-diagnosis. We too observed that a proportion of non-CCS in our cohort experienced psychological distress and lower HRQOL compared to their siblings. Therefore, future studies could explore the long-term impact of childhood cancer diagnosis of childhood cancer on both CCS and their siblings.

Opportunity for intervention

While no statistical difference was observed between CCS and their siblings in psychological distress and HRQOL, a notable proportion of CCS still experienced psychological distress and low HRQOL, which were only detected through the questionnaires. The routine use of formal screening tools should be considered to identify at-risk individuals, with proactive psychological interventions proving effective.³⁴ We support the latest clinical practice guidelines from the International Late Effects of Childhood Cancer Guidelines Harmonization Group, which advocate the routine surveillance of mood disorders symptoms such as depression, anxiety and psychological distress, starting from the first follow-up visit and continuing throughout the lifespan of CCS.³⁵ Further evaluation by mental health professionals is advised for CCS showing indications of mental health problems, with prompt referral for diagnosis and risk assessment.

Limitations

We acknowledge several limitations of this study. First, participants who were unable to independently fill the questionnaires due to neurocognitive impairments were excluded. While the number of participants excluded was low ($n=6$), there was a possibility that these participants had greater severities of late effects resulting in lower HRQOL. Future studies could include this population using caregiver-reported questionnaires for a more comprehensive representation. Second, self-reported questionnaires such as BSI-18 and MOS SF-36 may be influenced by self-report and social desirability bias, resulting in potential underestimation of distress.^{30,31} Longitudinal studies with mean scores across multiple time points could improve the accuracy of such results. Third,

although BSI-18 and MOS SF-36 are validated tools that are commonly used, they are generic in nature and used for screening. Future studies correlating the degree of psychological distress and HRQOL to an eventual diagnosis of psychiatric illnesses would be valuable. Finally, the limited sample size (especially in the siblings' group) stemmed from participant recruitment being confined to a single institution. Future studies can consider collaborating with a consortium of other institutions to increase the cohort size. This collaborative approach would enhance the cohort size, facilitating more robust and statistically rigorous results.

CONCLUSION

This study explored the long-term impact of childhood cancer on psychological distress and HRQOL of CCS in Singapore. Approximately a quarter of CCS reported psychological distress and 21.7% exhibited low mental health scores in HRQOL. There were no significant differences in psychological distress and HRQOL between CCS and their siblings when demographic factors were matched. Notably, a history of psychiatric illness and mood disturbances linked to the COVID-19 pandemic was associated with poorer scores in psychological distress and HRQOL. Therefore, in light of these findings, we strongly advocate regular surveillance of psychological distress and HRQOL among CCS in order to implement timely and appropriate interventions.

Declaration

This research received funding from the National University of Singapore. The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Ethics statement

The study was approved by the SingHealth Centralised Institutional Review Board (Reference number 2021/2404).

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