Long term outcomes of the Indian childhood cancer survivorship (C2S) cohort: a multicentre study (2016–2024)

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Summary

Background **Almost 90% of childhood cancers occur in lower income- and middle-income countries (LMICs) like India, leading to a growing population of cancer survivors. However, data on long-term outcomes and late effects are limited. The Indian Childhood Cancer Survivorship (C2S) Study was envisaged to build a nationwide survivor cohort and systematically capture treatment exposures and long-term outcomes.**

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Methods The C2S study is a prospective multicentric observational cohort initiated in 2016 under the Indian Pediatric Hematology Oncology Group (InPOG-LE-16-01). Children diagnosed with cancer before 18 years of age and in remission post-treatment were enrolled. Demographic, clinical, and treatment exposure data were collected at respective centres and monitored centrally. Follow-up was conducted every three months, assessing survival, relapse, and abandonment rates.

Findings As of December 2024, the study includes data from 20 centres across India with 5419 survivors being enrolled, with survival data available for 5140. Acute leukemia was the most common diagnosis (40.9%). Common therapeutic exposures included chemotherapy (94.7%), surgery (30.3%), and radiotherapy (26.3%). The 5-year overall survival (OS) and event-free survival (EFS) rates for the entire cohort were 94.5% (95% CI: 93.7–95.3)% and 89.9% (95% CI: 88.8–91.0)%, respectively. For the 2266 survivors with ≥2 years post-treatment follow-up, 5 y-OS and EFS were 98.2 (95% CI: 97.5–98.7)% and 95.7 (95% CI: 94.7–96.6)%, respectively.

Interpretation The C2S study represents the first structured attempt to build a nationwide childhood cancer survivors' cohort in India. This cohort will serve as a denominator for future research on late effects, support the development of survivorship guidelines, and inform policy planning in India and comparable LMIC settings.

Funding There was no dedicated funding for this study.

Keywords: Cancer survivor; Child; India; Multicentre study; Registry; Cohort

Research in context

Evidence before this study

A literature search was conducted using MEDLINE and PubMed to identify available childhood cancer survivor cohorts from low- and middle-income countries (LMICs), on the topic using keywords "childhood cancer survivors," "late effects," "long-term outcomes," "pediatric oncology," and "India" or "low- and middle-income countries (LMICs)". Published data on the prevalence of late effects in childhood cancer survivors from LMICs, including India, is limited. The information on the late effects from LMICs is limited to single-center studies from India, Egypt, Kenya, and other African nations, with the majority being retrospective, and limited by small sample sizes, short follow-up, and incomplete documentation of exposures. Although these studies have evaluated several individual late effects like, neurocognitive, endocrinological, and psycho-social morbidities, along with knowledge-attitude-practice evaluation, systematic mechanisms for longitudinal follow-up, monitoring of late-effects and understanding them in the context of exposures are lacking. Also, we could not find any multi-centric cohort of childhood cancer survivors from LMICs.

Added value of this study

This study describes the development and execution of the Indian Childhood Cancer Survivorship (C2S) cohort, one of the first prospective, multicentre childhood cancer survivor registry from a resource-limited setting in general and from India in particular. With over 5000 survivors enrolled from 20 geographically diverse centers across the country, it gives a detailed description of the cohort characteristics, treatment exposures (chemotherapy, radiotherapy, surgery), and follow-up. It also highlights the collaboration across public and private sector institutions across all four regions (east, west, north, and south) of the country. The findings underscore significant differences from well-established cohorts from high-income countries, due to a lower number of brain tumors, lower exposure to radiotherapy, and higher exposure to anthracycline.

Implications of all the available evidence

The cohort would form a denominator for the future multicentre research on childhood cancer survivorship in the country, as differences in exposures warrant local adaptations of the international guidelines in the regional context, with due consideration to the regional evidence. It would serve as a model for similar resource-limited settings, to engage in collaborative research in survivorship and to help in capacity-building for better post-treatment care to improve quality of life and reduce long-term morbidity/mortality in childhood cancer survivors.

Introduction

Strides have been made in the cure rates of childhood cancer with advances in the fields of diagnosis, supportive care and therapeutics. Improved survival translates into a growing population of childhood cancer survivors. In 1975, fewer than 50% of children

diagnosed with cancer before the age of 20 years survived in the United States for more than 5 years. Since then, results have greatly improved, and the US SEER data from 2004 to 2010 suggests that, more than 80% of children diagnosed with cancer before the age of 20 years survived at least 5 years.[1–3] Although these survival figures from high-income countries are often not replicated in lower income- and middle-income countries (LMICs), nearly 90% of children with cancer reside in these regions, leading to a rise in the population of cancer survivors in LMICs.[4]

Childhood cancer survivors are more likely to develop chronic health conditions,.[5,6] and interest and understanding in this field have expanded in recent years.[7] Several large cohorts of childhood cancer survivors have been established in Europe and North America, which have facilitated research on late effects and continue to provide the denominator for investigating long-term health-related consequences of childhood cancer treatment. Recently, there has been interest in *global mapping of survivorship services*, which projects the current landscape of cancer survivorship care, identifies and assesses the availability and effectiveness of services across different countries and regions, considering the diverse cultural and socioeconomic contexts.[8] This would, in addition, identify gaps in services, attempts towards access to comprehensive and effective support systems, with the ultimate aim of improving the quality of life of cancer survivors.

Late effects are likely to appear months or years after the completion of treatment. It is estimated that one-third to one-half of childhood cancer survivors will experience a long-term/late effect of cancer therapy, of which up to one-half may be life-threatening.[9,10] Several models of long-term follow-up care have also been developed in terms of who provides it, where, and how; the most popular being survivorship clinics. Recognition of the importance of appropriate multidisciplinary and cross-specialty care is increasing, especially for adolescent and adult survivors of childhood cancers.[11] Guidelines for long-term follow-up have been laid down by various national study groups, like the Children's Oncology Group, Scottish Intercollegiate Guideline Network (SIGN), United Kingdom Children's Cancer Study Group (UK CCSG), and the Dutch Children's Oncology Group (DCOG).[12,13] Attempts to develop such guidelines tailored to the Indian context, and other such settings with larger volumes but limited resources, are in the early phases of development.[14]

Despite this, there is very limited data on the prevalence of late effects in childhood cancer survivors from LMICs, including India. Registries for determining the incidence of childhood cancers do exist in India; however, there is very limited data on long-term follow-up and prevalence of late effects in survivors, and these are mostly limited to a single center,[15–17] there is an unmet need for establishing comprehensive nationwide childhood cancer survivor registry and a survivors' cohort in India to evaluate and improve their long-term health. Incidence-based registries include all patients at diagnosis, whereas survivor cohorts exclude early deaths, abandonment, and refractory disease, hence yielding deceptively higher survival estimates but facilitating capture of late effects. This cohort would provide evidence to enable accurate characterization of various late effects and long-term morbidities in this population.[18,19]

This study, the Childhood Cancer Survivorship (C2S) Study, was envisaged in two phases with distinct objectives. Phase *one* of the study was designed to establish a multi-centre registry and cohort for children completing treatment for childhood cancer. It would establish a systematic framework for maintaining a cohort to track statistics on childhood cancer survivors and support the development of a registry to retain all patients who have completed treatment and in complete remission. The registry would form the Indian Childhood Cancer Survivor (C2S) Cohort.

Phase two would focus on in-depth studies that will be directed at providing evidence on the strength and direction of the association of late effects with exposures on the Indian C2Scohort and would attempt to generate consensus statements for follow-up of childhood cancer survivors in India. The formation of the cohort, cohort characteristics, and major exposures are described in the current publication.

Methods

The C2S study is a prospective multicentric observational Indian Pediatric Haematology Oncology Group study (InPOG-LE-16-01) that was initiated in the year 2016. The duration of recruitment initially was five years, and the study has received extension till the year 2029.

Building of the study group

The study was planned by the Indian National Pediatric Oncology Group (InPOG), which started in the year 2008, with the primary aim to carry out nationwide collaborative research. Under InPOG, the late effects subcommittee, which was formed in 2015, and the Childhood Cancer Survivorship Study (C2S study) was launched in the year 2016. Later, the name of the subcommittee was changed to the 'Survivorship and late effects subcommittee'. The C2S study was first approved by the subcommittee members and then subjected to reviews by national and international experts in this field. In the year 2019, benign haematology was added to the research group InPOG, and its name was changed to the Indian National Pediatric Haematology Oncology group (INPHOG).

Centres were invited by email to participate in the study. Since 2023, INPHOG has provided clinical research coordinators to some of the participating centers in the C2S study.

Data collection, transfer, and central monitoring

Before initiating data collection, training was provided to personnel involved in data management at all centers. At study initiation, data were collected on physical case record forms and excel sheets at the local principal investigator (PI) site at each enrolment centre. Each local PI had access to the identity of patients from only their centre only. Transition to the electronic database was done in the year 2019. All centres were encouraged to maintain their data offline as well. Data entered (online/offline) by staff other than the local PI was validated by Principal Investigator periodically.

Each institution was provided a unique ID and was responsible for entering de-identified patient data directly into the platform using a predefined template with standardized variables to ensure uniformity. After the data was transferred in real-time to the central coordinating centre at New Delhi, the latter served as the data storage and management hub for the study. The central team conducted periodic quality checks to verify the completeness, consistency, and uniformity of the submitted data. In case of any discrepancies, missing values, or potential misreporting, official feedback was communicated back to the contributing centers via virtual meetings, email, or inbuilt query-resolution system. This process ensured high data fidelity and minimized errors before final analysis. Periodic meetings were held to discuss the difficulties faced by the participating centers and were attended by all site-specific PIs, the central PI, centre coordinators, technical staff, and data entry operators. Data access was role-based and governed by institutional permissions, with centralized oversight to ensure compliance with ethical and data protection standards.

Patient screening, enrolment, and follow-up

Patients were enrolled only after completing primary therapy and confirmed to be in remission, which by design excludes patients with early mortality, treatment abandonment (defined as discontinuation of therapy before planned completion), or disease progression during therapy.

Inclusion criteria

1. Children ($\leq$18 years of age at diagnosis) having completed treatment for cancer and in complete remission
2. Children treated at other centers with a complete treatment summary may be enrolled at the discretion of the treating physician, provided the patient is willing to participate in follow-up at the recruiting centre
3. Documentation of complete remission before enrolment by the most appropriate investigations
4. The demographic and clinical details of patients should be noted within 6 months of treatment completion in the proforma provided.

Exclusion criteria

1. Patients/guardians not consenting to long-term follow-up.
2. Patients with relapsed or progressive disease.

The primary oncologist counselled the participants regarding the importance of follow-up after treatment completion. A patient information sheet was provided. Consent/assent for enrolment was taken. Study-proforma was filled within six months of completion of treatment.

Demographic details captured included the full name, sex, and study ID. e.g. (InPOG-LE-16-01- *AIIMS*-01), institute name, date of birth (age at diagnosis was recorded for patients where date of birth was not available), father's name and Aadhar card (government identity card) number, and socio-economic status as per the modified Kuppuswamy classification based on education, profession and income of the head of the family. Contact address included local and permanent address of the family or close relative. Telephone/mobile numbers of both the parents or close relatives and, e-mail address (optional) were recorded. Contact details were updated at each visit.

The online proforma had a drop-down list of common childhood cancers to aid uniform collection of data on diagnosis (cancer type), date of diagnosis and completion of therapy. Treatment exposures included: chemotherapy (Yes/No), list of chemotherapy drugs and cumulative doses of adriamycin, daunorubicin, cyclophosphamide, ifosphamide, bleomycin, etoposide, high-dose methotrexate (single dose>1000 mg/m^2), high-dose cytarabine (single dose >1000 mg/m^2) and intrathecal chemotherapy. Details of radiation exposures included: exposure (Yes/No), site, field, and total dose. Surgical details included: exposure (Yes/No), name of procedure, and site (if applicable, laterality). Other details recorded were transfusion requirements, hematopoietic stem cell transplant, and viral serology status (Hepatitis B, C, and HIV).

Clinical data included records of growth (weight, height at each visit), pubertal status (Tanner stage), disease status, and school/college attendance. A general physical examination was carried out at each visit. Cardiac, pulmonary, and other relevant assessments were done depending on disease and exposures, and were done at the discretion of the principal investigator. All patients were provided with a treatment summary and follow-up plan at the time of enrolment. Patients were counselled regarding the need for regular follow-up and the importance of healthy lifestyle.

Patients were followed every 3 months for the first 2 years and every 6 months thereafter, using physical or telephone contact to ascertain vital status. The database was updated at least once in six months. Data updated in each visit included the following: updated contact details, alive Yes/No (date in case of event), disease relapse Yes/No (date in case of event), weight (kg), height (cm), tanner stage, school/college attendance yes/no, new symptoms (if yes, details like: exercise intolerance, chronic cough, jaundice, fatigue, lethargy and psychosocial etc.) as free text. Patients with missed follow-up visits were tracked down telephonically.

Statistical analysis

At the end of the study, we expected to have the number and proportion of survivors who are at least 2 years off therapy and in continued remission.

Descriptive analysis was carried out to find out frequencies and percentages. Outcome was evaluated using Kaplan–Meier analysis to calculate survival as well as failure estimates. Event-free survival (EFS) was defined from the date of diagnosis until the time of first event (progression/relapse of disease, or death resulting from any cause) or last follow-up and overall survival (OS) was defined from the date of diagnosis to the date of death due to any reason. Reported OS/EFS reflect outcomes after completion of therapy and are therefore not incidence-based survival estimates.

Lost to follow-up was defined as patients who did not have any follow-up for more than 12 months, but their outcomes were analysed while censoring their outcomes on the day of last contact. All the outcomes were censored as of 31st December 2024. The data were analysed using STATA statistical software for Windows version 12.0 (StataCorp, College Station, TX, USA). A p-value less than 0.05 was considered statistically significant.

Ethical statement

The ethical clearance for study was taken from AIIMS ethics committee and received on 21.06.2016; IEC-315/07.06.2016, RP-15-2016.

Enrolment at each centre started after getting Individual Institutional Ethical Committee (IEC) approval. All patients and/or their parents or legal guardians signed a written informed consent in English/Hindi or local language before being enrolled in the study.

Role of the funding source

This study did not receive external funding. Since 2023, INPHOG has provided clinical research coordinators to some of the participating centers in the C2S study.

Results

A total of thirty-one centres distributed across the east, west, north, and south zones of the country had shown interest in participating in the study. Twenty-seven centres had obtained ethical clearance for participation at the time of data analysis, of which twenty centres have started recruiting patients; seven centres have obtained ethical clearance and are receiving training to start patient recruitment. In addition, four centres are in the process of obtaining ethical clearance. The centres entered into the study at varying time points, with centre details, years of inclusion in the study, and number of patients per centre as shown in Table 1 and Fig. 1.

The total number of participants enrolled in the cohort is 5419, of which the survival outcome is available for 5140 patients. The number of patients enrolled per centre varies from a minimum of 25 to a maximum of 1152, with a median of 168 patients enrolled per centre. Sixteen centres have completed two years of follow-up since treatment completion, for at least a proportion of patients (n = 2266, 41.8%). Out of all the patients enrolled, 1928 (35.6%) have completed at least five years of follow-up from diagnosis, and 793 (14.6%) since treatment completion. Among the entire enrolled cohort (N = 5419), common diagnoses were acute leukemia (40.9% with 34.4% being acute lymphoblastic leukaemia), Hodgkin lymphoma (12.9%), retinoblastoma (7.4%), and bone tumors (8.4%). Forty-four percent of survivors were between age 2 and 8 years. The majority were males and belonged to upper-lower socio-economic strata as evaluated by the modified Kuppuswamy scale. Patient demographic profiles are depicted in Table 2.

Across geographic regions, the significant association with sex distribution (χ^2 = 47.3, p = 0.000) was driven by a higher proportion of male patients recruited from the centres based in the northern and western area of the country compared with relatively balanced sex ratios reported by centres based in the south and eastern area of India (Supplementary Tables S1 and S2). The diagnostic profile varied significantly by region (χ^2 = 66.1, p = 0.000), with a higher proportion of ALL in the southern centres and a markedly higher proportion of retinoblastoma in the eastern and northern centres due to one of the participating centers being the National Center of Excellence in ophthalmology. differences were also evident in socioeconomic status (χ^2 = 21.6, p = 0.001), with a higher proportion of lower-SES patients in the southern and western centres, attributed to predominant participation of government/public sector institutions in those areas (χ^2 = 505.3, p = 0.000).

Treatment exposures were analyzed for the entire cohort and are summarized in Table 3. Chemotherapy was the most common form of therapeutic exposure received by 94.7% patients, followed by surgery (30.3%) and radiotherapy (26.3%). Commonest drug exposures were cyclophosphamide (48.1%), anthracycline (43.4% doxorubicin and 30.2% daunorubicin), followed by etoposide (22.6%).

Sr no.	Region	Participating centers	Enrolment (N = 5419)	Percentage
1	North	All India Institute of Medical Sciences, New Delhi	1152	21.26
2		Rajiv Gandhi Cancer Institute, New Delhi[a]	807	14.89
3		Indraprastha Apollo Hospital, New Delhi[a]	356	6.57
4		Safdarjung Hospital, New Delhi	133	2.45
5		Max Super Specialty Hospital, Saket, New Delhi[a]	115	2.12
6		Max Super Specialty Hospital, Patparganj[a]	34	0.63
7		Kalawati Saran Children's Hospital, New Delhi	40	0.74
8		Post Graduate Institute of Child Health, Noida	101	1.86
9		King George's Medical University, Lucknow	388	7.16
10	South	Apollo Hospital, Chennai[a]	185	3.41
11		Cancer Institute, Adyar, Chennai	168	3.10
12		Kidwai Memorial Institute, Bengaluru	624	11.52
13		MVR Cancer Centre and Research Institute, Kerala[a]	62	1.14
14		Rainbow Children's Hospital, Hyderabad[a]	74	1.37
15		Regional Cancer Centre, Thiruvanthapuram	328	6.05
16		Kasturba Medical College, Manipal[a]	96	1.77
17	West	Tata Memorial Hospital, Mumbai	505	9.32
18		Lokmanya Tilak Municipal Medical College	185	3.41
19	East	Tata Medical Centre, Kolkata[a]	41	0.76
20		All India Institute of Medical Sciences, Bhubaneshwar	25	0.46
In process[b]				
21	North	Banaras Hindu University, Varanasi		
22		Dayanand Medical College, Ludhiana		
23		All India Institute of Medical Sciences, Jodhpur		
24		Dr. Ram Manohar Lohia Delhi		
25	South	Basavatarakam Indo-American Cancer Hospital and Research Institute[a]		
26		St. John's Medical College, Bengaluru[a]		
27	West	Wadia Hospital, Mumbai		
Prospective center[c]				
28	South	Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry		
29		Sri Shankara Cancer Hospital Bengaluru[a]		
30		Sri Ramachandra Medical College, Chennai[a]		
31	West	MCGM-Comprehensive Thalassemia Care, Pediatric Hematology-Oncology & BMT Borivali, Mumbai Centre[a]		

[a]Private sector hospitals, while the rest are public sector or trust hospitals. [b]Centers that got IRB approval and are in process of receiving training. [c]Centers in process of getting IRB approval.

Table 1: **Statistics of centers enrolled in the C2S study.**

Most surgical exposures were received for bone tumors (20.4%), retinoblastoma (18.9%), and renal tumors (13.4%); while ALL (20.3%), Hodgkin lymphoma (17.2%), and bony sarcoma (13.9%) dominated the radiotherapy-exposed group. Out of those who received radiotherapy, head and neck (17.9%) was the most common site of radiation, followed by brain (15.6%) and abdomen (14.2%).

Combined exposures were received by 47.1% survivors, out of which most were chemotherapy plus surgery (27.2%), followed by chemotherapy and radiotherapy (22.9%), while 11.1% patients received all three forms of therapy. Blood component therapy was received by 57.6% survivors, and hematopoietic stem cell transplant (HSCT) was done for 1.9% patients.

Median period of follow-up from diagnosis is 3.9 (IQR, 2.3–6.2) years and from treatment completion is 1.6 years (IQR, 0.5–3.5) for the whole cohort. For patients who have completed a minimum of two years from treatment completion, the median period of follow-up from diagnosis and treatment completion is 6.4 (IQR, 4.9–7.8) and 3.9 (IQR, 2.8–5.8) years, respectively. As of 31st December 2024, out of 5140 patients for whom survival outcomes are available, 92.0% (n = 4730) are alive in remission without any history of relapse. Death occurred in 254 (4.9%) during follow-up, while 291 (5.7%) survivors relapsed, and 481 (9.3%) survivors were lost to follow-up. Out of 2266 patients who have completed a minimum of two years from treatment completion, 93.9% (n = 2128) are alive in remission. Death occurred in 80 (3.5%) survivors during follow-up, while 64 (2.8%) relapsed, and 213 (9.4%) survivors were lost to follow-up.

The 5-year overall survival (OS) and event-free survival (EFS) for the entire cohort were 94.5 (95% CI: 93.7–95.3)% and 89.9 (95% CI: 88.8–91.0)%, respectively. For the 2266 survivors with ≥2 years post-treatment follow-up, 5 y-OS and EFS were 98.2 (95% CI: 97.5–98.7)% and 95.7 (95% CI: 94.7–96.6)%, respectively. The corresponding failure curves are presented in Fig. 2 to provide a more accurate representation of the cumulative incidence of adverse outcomes over time. Supplementary Table S3 demonstrates that survival outcomes varied significantly, with both OS and EFS differing across regions. While no significant differences in OS were observed by socioeconomic status, EFS since treatment completion was lower in the lower SES group (p = 0.011).

Discussion

This study is a systematic attempt to develop a childhood cancer survivorship (C2S) cohort in India with the intent of describing long-term survivor outcomes and treatment exposures. It creates a multi-institutional model for survivorship research in LMICs that can be expanded upon with future new survivors enrolled from additional geographically and administratively distinct pediatric oncology centers. This survivor cohort will form the basic platform on which many other studies will be conceptualized.

This cohort of survivors, developed via multicentre collaboration and extensive stakeholder involvement, provides an example of a coordinated approach, uses standardized definitions of survival outcome and treatment exposures, with a heterogeneous cohort that reflects the different types of cancers, treatment practices, and post-treatment follow-up in India, and provides information about long-term outcomes in a real-world LMIC setting. Globally, large-scale cohorts of

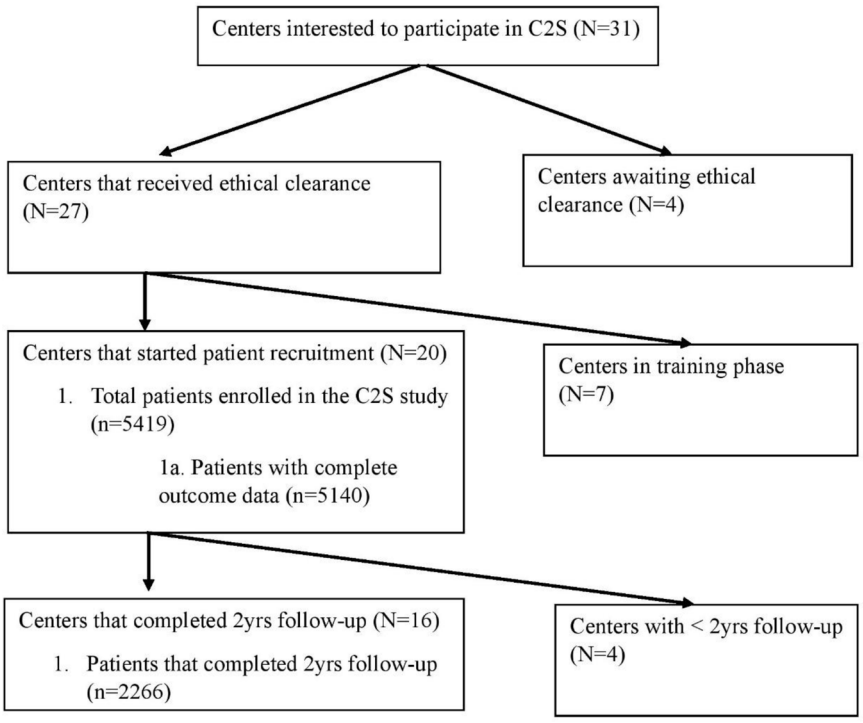

Fig. 1: **Schematic depiction of centers and patient cohorts at various stages of enrolment. Note: N, Indicates number of centers; n, Indicates number of patients.**

childhood cancer survivors have contributed to our knowledge of late effects after childhood cancer, cancer-specific and all-cause mortality trends, and neuro-psychosocial consequences after childhood cancer. The CCSS in the US, established in 1994, recruited over 35,000 childhood cancer survivors diagnosed between 1970 and 1999 at 31 institutions, and had detailed data on late effects based on longitudinal follow-up.[20] Similarly, the St. Jude Lifetime Cohort Study (SJLIFE), British Childhood Cancer Survivor Study (BCCSS), and Adult Life after Childhood Cancer in Scandinavia (ALiCCS) cohorts from the US, UK, and Nordic countries, respectively, provide informative data from similar registry-linked studies.[19,21,22] Our cohort characteristics differ from these international cohorts in several aspects, for example, the representation of brain tumors in the C2S cohort is limited to only 3.8%, compared to approximately 10% in both the CCSS and SJLIFE cohorts, likely because most brain tumors in India have historically been treated by radiation oncologists rather than pediatric oncologists, leading to underrepresentation in pediatric cancer registries.[1,18] The limited salvageability of high-grade brain tumors, like glioma, ependymoma, and high-risk medulloblastoma in the country could have also contributed to this difference. Only 26.3% of patients in the C2S cohort received radiotherapy in contrast to more than 50% in CCSS, likely reflecting both the lower incidence of brain

	Number	Percent
A) Diagnosis as per International Classification of Childhood Cancer, 3rd Edition (ICCC-3)		
I. Leukemias, Myeloproliferative and Myelodysplastic Diseases	2266	41.82
a. Lymphoid leukemias	1862	
b. Acute myeloid leukemias	328	
c. Chronic myeloproliferative diseases	2	
e. Unspecified and other specified leukemias	74	
II. Lymphomas and Reticuloendothelial Neoplasms	**1020**	**18.82**
a. Hodgkin lymphomas	701	
b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	212	
c. Burkitt lymphoma	88	
e. Unspecified lymphomas	19	
III. CNS and Miscellaneous Intracranial and Intraspinal Neoplasms	**206**	**3.80**
a. Ependymomas and choroid plexus tumor	13	
b. Astrocytomas	23	
c. Intracranial and intraspinal embryonal tumors	118	
e. Other specified intracranial and intraspinal neoplasms	17	
f. Unspecified intracranial and intraspinal neoplasms	35	
IV. Neuroblastoma and Other Peripheral Nervous Cell Tumors	**138**	**2.55**
a. Neuroblastoma and ganglioneuroblastoma	136	
b. Other peripheral nervous cell tumors	2	
V. Retinoblastoma	**401**	**7.40**
VI. Renal Tumors	**250**	**4.61**

(Table 2 continues on next page)

		Number	Percent
(Continued from previous page)			
a. Nephroblastoma and other non-epithelial renal tumors		192	
c. Unspecified malignant renal tumors		58	
VII. Hepatic Tumors		**53**	**0.98**
a. Hepatoblastoma sarcoma and mesenchymal tumors of liver		53	
VIII. Malignant Bone Tumors		**456**	**8.41**
a. Osteosarcomas		158	
c. Ewing tumor and related sarcomas of bone		279	
d. Other specified malignant bone tumors		19	
IX. Soft Tissue and Other Extraosseous Sarcomas		**212**	**3.91**
a. Rhabdomyosarcomas		147	
b. Fibrosarcomas, and other fibrous neoplasms		9	
d. Other specified soft tissue sarcomas		34	
e. Unspecified soft tissue sarcomas		22	
X. Germ Cell Tumors, Trophoblastic Tumors and Neoplasms of Gonads		**169**	**3.12**
a. Intracranial and intraspinal germ cell tumors		2	
c. Malignant gonadal germ cell tumors		164	
d. Gonadal carcinomas		3	
XI. Other Malignant Epithelial Neoplasms and Malignant Melanomas		**32**	**0.59**
a. Adrenocortical carcinomas		5	
c. Nasopharyngeal carcinomas		26	
e. Skin carcinomas		1	
XII. Other and Unspecified Malignant Neoplasms		**184**	**3.39**
a. Other specified malignant tumors		112	
b. Other unspecified malignant tumors		72	
Missing data		**32**	**0.59**
B) Age group of survivors at the time of diagnosis			
0–2 yrs		1019	18.80
2.1–8 yrs		2413	44.53
Above 8 yrs		1759	32.46
Missing		228	4.21
C) Sex distribution			
Male		3537	65.27
Female		1812	33.44
Missing		70	1.29
D) Socio-economic status (Kuppuswamy socioeconomic class)			
Lower		139	2.57
Upper lower		1139	21.02
Lower middle		372	6.86
Upper middle		194	3.58
Upper		206	3.80
Missing		3369	62.17
E) Public or private sector institution			
Government/public sector		3649	67.34
Private sector		1770	32.66
F) Follow-up period		**Median (years)**	**IQR (years)**
For the entire cohort	From diagnosis	3.9	2.3–6.2
	From treatment completion	1.6	0.5–3.5
For the cohort with 2 years from treatment completion	From diagnosis	6.4	4.9–7.8
	From treatment completion	3.9	2.8–5.8

Table 2: **Diagnosis and demographic profile of subjects enrolled in the C2S study (N = 5419).**

A) Details of individual exposures		
Exposure	**Number**	**Percent**
Chemotherapy	5130	94.67
Surgery	1639	30.25
Radiotherapy	1423	26.26
Hematopoietic stem cell transplant	105	1.94
Blood products	3121	57.59
Name of chemotherapy drugs	**Number**	**Percent**
Bleomycin	615	11.35
Carboplatin	612	11.29
Cisplatin	447	8.25
Cyclophosphamide	2605	48.07
Any anthracycline	3202	59.09
Daunorubicin	1635	30.17
Doxorubicin	2353	43.42
Dacarbazine	571	10.54
Etoposide	1225	22.61
Ifosphamide	557	10.28
Sites of radiation therapy[a]	**Number (n = 1423)**	**Percent**
Abdomen	202	14.20
Brain	222	15.60
CSI	113	7.94
Head/Neck	255	17.92
Limb	101	7.10
Spine	30	2.11
TBI	8	0.56
Testis	2	0.14
Thorax	120	8.43
Orbit	112	7.87
Others	258	18.13
B) Details of combined exposures	**Number**	**Percent**
Chemotherapy + radiotherapy	1242	22.92
Chemotherapy + surgery	1476	27.24
Surgery + radiotherapy	627	11.57
Chemotherapy + surgery + radiotherapy	603	11.13
Single modality exposures	2871	52.98

[a]All % are mentioned as proportion of the whole cohort (N = 5419), while % of radiotherapy sites are expressed as proportions of the cohort that received radiotherapy (n = 1423).

Table 3: **Therapeutic exposure profile of subjects enrolled in the C2S study (N = 5419).**[a]

tumors in our cohort and the fact that C2S represents a more recent treatment era when the indications for radiotherapy have been significantly tailored.

Anthracycline exposure in our cohort was higher (59.1%) than that in CCSS (45%), likely due to a higher proportion of haematolymphoid cancers in our cohort. The high 5-year OS/EFS observed in our study aligns with the survivor cohort design, where enrolment occurs post-treatment completion. As one of the earliest cohorts from LMIC and likely the first from an Asian country, the Indian C2S cohort presents several features that are unique. First, it gathers data from a resource-constrained setting in which access to follow-up care is inconsistent and data collection and tracking infrastructure are immature. Additionally, treatment costs in India vary widely between government and private hospitals, with government facilities providing highly subsidized or free care, while private-

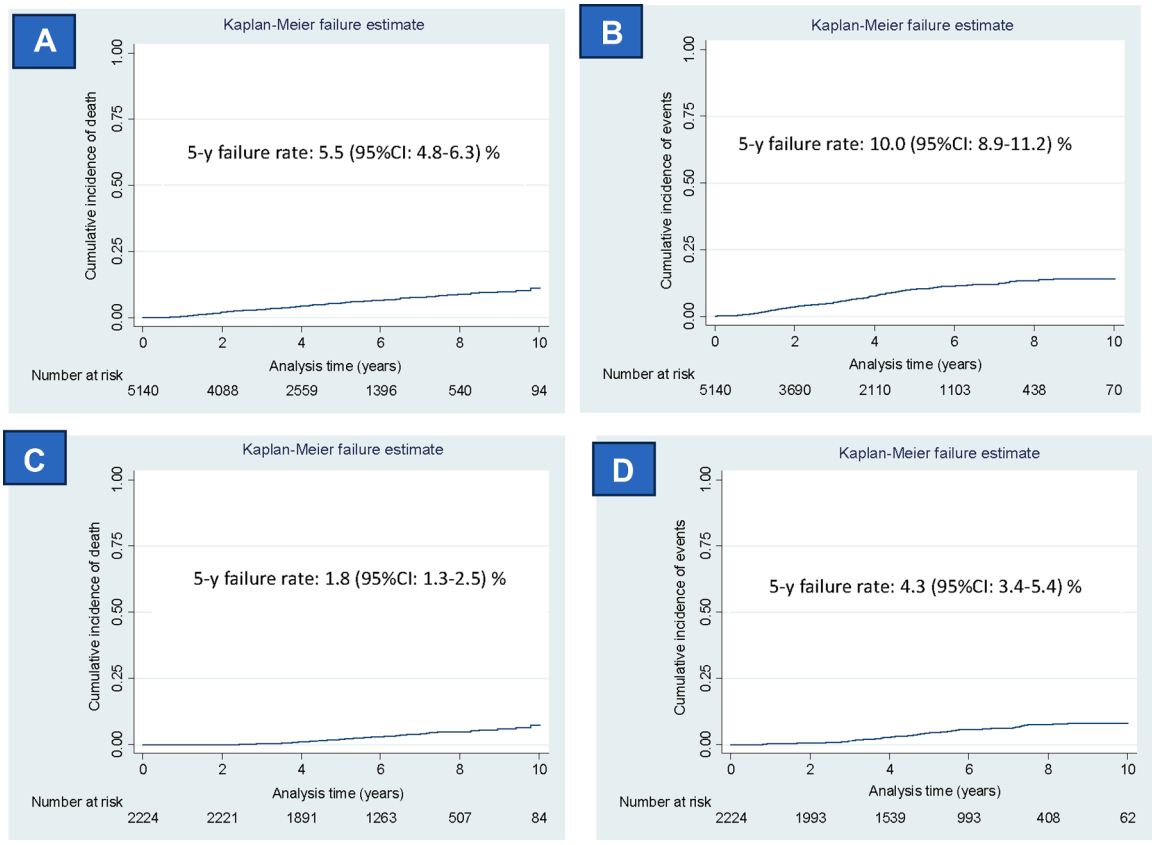

Fig. 2: **Kaplan Meier failure estimates for cumulative incidence of (A) death, and (B) event for the entire cohort; and of (C) death, and (D) event for the cohort that completed 2 years from the end of therapy**.

sector treatment often involves out-of-pocket expenditure, influencing health-seeking behavior and long-term follow-up. Second, the inclusion of patients treated in both public-sector institutions and in the charitable/private sector provides an adequate cross-section of the national cancer burden. Third, the variation in treatment exposures with respect to anthracycline use, omission of radiotherapy according to low-resource contexts, and modified regimens allows for a different lens through which to study treatment-outcome relationships in LMICs. It also reflects disease-specific referral patterns to particular centres.

When compared with the overall childhood cancer profile in India derived from hospital-based cancer registries, the C2S cohort represents a selective subset enriched for diagnoses with higher treatment completion and survival.[23] While registry data indicate that leukemias constitute approximately 36–40% and CNS tumors around 10–11% of childhood cancers in India, the C2S cohort shows a comparable or higher proportion of leukaemia (40.9%) but marked underrepresentation of CNS tumors (<4%). This divergence reflects differential salvageability, and survivorship bias inherent to post-treatment enrolment, whereby early deaths, treatment abandonment, and refractory disease are excluded. Consequently, survival estimates from C2S are not directly comparable to incidence-based registry survival but instead characterize the treatment exposure patterns and long-term outcome profile of childhood cancer survivors in the Indian context.

Additionally, this cohort serves to inform policy-relevant research with respect to childhood cancer survivorship. Survivorship was a neglected domain till a few years ago. Cancer survivors in India are often overlooked because there are few dedicated long-term follow-up systems in place. This study initiates a robust structure for survivorship care pathways, demonstrates the need for national guidelines, and identifies a role for primary care.

While developing this cohort, we faced several challenges. Centre recruitment was slow at the start of the study. The Covid-19 pandemic further impacted the study in terms of new centre recruitment and data acquisition from centers already recruited in the study. The most important challenge was that this was a non-funded study. Most centres were utilizing staff from other ongoing studies. Tracking of survivors was complicated by patients

returning to their hometowns with poor connectivity, the absence of electronic health records, and disconnected health-seeking behavior. Variation in data quality (including treatment details) and the way outcomes were ascertained made quality assurance procedures and possibly electronic harmonization platforms essential for the future. Lately, INPHOG has provided clinical research coordinators (CRCs) to many centres participating in the C2S study, which has improved the quality of data entry, patient tracking, and ensured follow-up visits. The PICASSO (Partnership in cancer survivorship optimization) initiative by the Indian Cancer Society has also facilitated the C2S study via providing psycho-oncologists in centres having ACT clinics, who additionally contributed to data maintenance.

The limitations to our research include the lack of uniformity in the collection of late effects data, socio-economic status, detailed characteristics of the lost-to-follow-up cohort and limited representation of some defined subpopulations (e.g., brain tumors and post-stem-cell transplant patients). Work is ongoing to incorporate electronic tracking, mobile follow-up tools, capture of detailed socio-economic information and build collaboration with national health databases to improve the completeness of the data and longevity of the cohort. We also acknowledge that our OS/EFS estimates are subject to survivorship bias, as already explained and hence not directly comparable to incidence-based cancer registries. Despite these challenges and limitations, many strengths forecast the long-term applicability of this cohort. It is one of the first LMIC-based survivor datasets to have harmonised baseline and treatment exposure variables across multiple centres. It is a prospective cohort, unlike other American and European cohorts. It enables investigations of key areas, such as life expectancy, geographic and regional disparities, and access to healthcare after therapy. Additionally, we have provided a model for other LMICs to follow in their development of survivorship registries with minimal increases to incremental costs, especially through instilling survivorship tracking as part of standard clinical practices and follow-up.

In conclusion, this cohort paves the way towards addressing the evidence gap on childhood cancer survivorship in lower income and middle-income countries–providing a means to explore long-term outcomes, treatment exposures, and late effects in the Indian context. The study demonstrates the feasibility of data collection across diverse centers he study demonstrates the feasibility of data collection across diverse centers and highlights substantial heterogeneity in survivorship with respect to centre and cancer-type.

Contributors

RS, GK, and RA conceptualized the study. RS, DM, and AS did the analysis and wrote the first draft of the manuscript. VR,RA,NRM,GD,MP, JPM, and AKG provided critical inputs to the manuscript. CK was involved in handling and training staff for online data capture. All including PKau, NV, AM, PT, NR, RR, SS, SR, PB, YK, PM, EAR, PJ, DS, DM, VG, GS, SK, PP, AKAR, PMal, CK, SD, SKA, VP, PKan, MP, JC, PKur, were involved in data curation, investigation. RS and DM and AS have directly accessed and verified the underlying data reported in the manuscript.

All authors approve the content of manuscript.

Data sharing statement

Data would be available on reasonable request from the corresponding author.

AI use disclosure

The authors used ChatGPT version 4 by OpenAI to improve language and clarity. All content was verified by the authors.

Declaration of interests

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2026.100727.

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