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original reports abstract

Long-Term Outcomes in Survivors of Childhood Cancer: A 30-Year Experience From India

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PURPOSE Despite an increasing number of survivors of childhood cancer (CCS) in low- and middle-income countries, survivorship care is in its nascent stages. We describe the spectrum of late effects seen, challenges faced, and lessons learnt over three decades of a late effects program in India.

METHODS We describe the demographics and profile of late effects of all CCS survivors enrolled in our After Completion of Treatment Clinic from February 5, 1991 (inception) to February 4, 2021. We analyzed the trends by the decade of diagnosis.

RESULTS There were 3,067 CCS survivors, the median age was 18 years (range, 3-57 years), and the median follow-up was 11 years (range, 2-46 years). Two thirds (62.4%) had either no or mild late effects, 480 (15.6%), 497 (16.2%), and 162 (5.3%) had grades 2, 3, and 4 late effects, with 67 deaths reported. Notable late effects were chronic viral hepatitis (7.8%), thyroid dysfunction (7.5%), other endocrine issues (13.6%), psychosocial issues (57%), neurocognitive impairment (4.1%), and metabolic syndrome (4%). The cumulative incidence and severity of late effects showed a consistent decline by the decade of diagnosis. Twenty-two percent of survivors are lost to follow-up.

CONCLUSION Survivors of childhood cancer treated on contemporary treatment protocols have a significantly lower side-effect profile. Attrition to long-term follow-up and psychosocial issues are significant concerns. Understanding the unique spectrum of late effects and establishing a holistic support system go a long way in ensuring the long-term physical and mental health and psychosocial concerns of childhood cancer survivors in low- and middle-income countries.

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BACKGROUND

An estimated 52,366 children (0-14 years) and 76,805 children and adolescents (0-19 years) develop cancer every year in India.[1] Although the great leaps in childhood cancer survival from the West have not been replicated in India and other low-middle income countries (LMICs), there has been a modest improvement in survival.[2] With the focus being improvement in cure rates, survivorship has not been a priority until recently.[3] This is unfortunate since it is well recognized that survivors of childhood cancer might have a high and varying risk of developing long-term health conditions.[4-6] The prevalence of late effects increases as time from cancer diagnosis elapses (beyond the fourth decade of life) such that by age 50 years, survivors experience an average of 4.7 chronic health conditions of grade 3-5, double that of age-matched controls.[4-6]

Although there is increasing interest in survivorship care in India in the past few years, this field is still in its nascent stages.[3,7] A recent comprehensive review described how several centers have initiated late effects services, predominantly within larger pediatric oncology units, often catering to children and adolescents with a relatively short duration of follow-up. The past decade has also seen advocacy by nonprofit organizations and the emergence of an active late effects subcommittee in the Indian Paediatric Oncology Group.[3]

The After Completion Treatment (ACT) Clinic at Tata Memorial Hospital, Mumbai, is the oldest and largest survivorship clinic in India, established in 1991 after a similar initiative at the St Jude Research Hospital, USA. The clinic coordinates the care of a large proportion of survivors with late effects requiring intervention. As of 2021, the Clinic caters to more than 3,000 long-term survivors of childhood cancer.[3,7-9]

Importantly, as the first such survivorship clinic in India, the ACT Clinic has been instrumental in mentoring several centers in starting late effects services. We hypothesized that the burden of late effects in our population is different from that in the West and aimed

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Does the profile of late toxicities in long-term survivors of childhood cancer in India differ from the West? Have there been any notable changes over the decades?

Knowledge Generated

In 3,067 survivors of childhood cancer, more than one third had late effects requiring intervention. Notable late effects were transfusion-transmitted infections, endocrinopathies, psychosocial issues, and metabolic syndrome. Attrition to follow-up is a major concern. There was a consistent decline in the late effect profile by the decade of diagnosis.

Relevance

Understanding the unique spectrum of late effects and multifactorial etiology helps ensure holistic and sustainable support for survivors of childhood cancer.

to assess the burden of late effects in childhood cancer survivors registered at our clinic and to identify the population at a higher risk of developing late effects. This article also describes the stages of development of the Clinic.

METHODS

Setting and Participants

The Pediatric Oncology Unit at the Tata Memorial Centre is the largest such unit in India, and sees close to 2,500 children (age $<$ 18 years) annually. The ACT Clinic is part of the pediatric oncology unit and is currently situated in a separate area within the routine clinic. Only children (age at diagnosis $<$ 18 years) who have received complete treatment at our center are eligible. Until 2013, children 2 years after completion of treatment and in remission were eligible. In 2013, because of the large volume of patients, the inclusion criteria were amended to make only children age 5 years from initial diagnosis of cancer eligible. Patients who had relapsed previously need to be in remission for at least 2 years after salvage treatment.

Although the clinic was initially conducted once weekly, since 2017, the clinic is conducted twice weekly, and walk-in appointments are seen on all days. The clinic is coordinated by pediatric oncologists; in addition, all survivors are seen by psychologists, dieticians, and social workers attached to the clinic. Selected survivors are assessed by radiation oncologists, surgical oncologists, and ophthalmologists.[8,9] Since 2016, dedicated clinics for cardio-oncology and endocrinology follow-up of survivors of childhood cancer are functional within the hospital.[10] The ACT Clinic co-ordinates the care of a large proportion of survivors with late effects requiring intervention and is part of the successful holistic support group at Tata Memorial Hospital.[11] Collaborations with nonprofit organizations and other donors have helped the ACT Clinic expand its rehabilitation-focused services to offer financial, psychosocial, educational, and vocational support, crucial to our population of survivors (Table 1).

Evaluation of Late Effects, Data Collection, and Extraction

Survivors are evaluated using a modified version of the international guidelines (Data Supplement).[12] Late effects are graded using an adapted version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).[13] The grading is as follows: grade 0: Normal; grade 1: mild symptoms; clinical or diagnostic observations only; intervention not indicated; grade 2: Moderate; minimal, local or noninvasive intervention indicated; grade 3: Severe or medically significant but not life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care; grade 4: life-threatening consequences; urgent intervention indication; and grade 5: Death related to AE.[13] Although grades 1-3 and 5 may refer to late effects involving any organ or system, grade 4 in our context predominantly involves late recurrences and second malignant neoplasms. Cumulative doses of anthracyclines and alkylating agents are calculated as per standard recommendations .[14,15] These data are recorded and updated at every visit in the Clinic Database, which is maintained on SPSS. Data of all survivors registered in ACT Clinic between February 1991 and February 2021 were retrieved retrospectively from case files, the database of ACT Clinic and Electronic Medical records. Data included clinical, demographic and treatment details (including cumulative doses), investigations, and details of late effects. History of any health problems attributable to cancer diagnosis or treatment or because of other causes was noted. For the purpose of this article, the survivors were analyzed by the decade of diagnosis (1971-1980, 1981-1990, 1991-2000, 2001-2010, and 2011 onwards), and the cumulative incidence of the commonly encountered late effects was compared. Survivors were considered lost to follow-up if a time period of at least 5 years had elapsed since their last clinic visit or virtual/online consultation. A cohort of 625 survivors from our center was previously described in 2003.[8,9] The late effect profile of this cohort was updated as of 2021 and compared with the original description.

Statistical Analysis

Results for continuous variables are expressed as median with range or mean (± standard deviation), and categorical variables are expressed using frequencies and percentages. For comparison of trends in cumulative incidence of late effects, a P value $<$ .05 was considered significant, and all P values were two-sided. All statistical analyses were

TABLE 1. Timeline of Development of ACT Clinic and Holistic Support

	Decade		
	1991-2000	2001-2010	2011-2021
Composition and function of ACT clinic	Establishment of multidisciplinary survivorship program—led by two pediatric oncologists and psychologists, and allied specialists Risk-based care Detailed treatment summary and dynamic surveillance plan Service mode—comprehensive in-person evaluation Focus on rehabilitation	Shifting focus to adolescent and young adult survivors of childhood cancer Liaison with specialists and NGOs Formation of peer-support group of AYA survivors	Addition of dietician, nurse, and data manager to the team In-house specialty clinics: cardio-oncology and endocrinology clinic. Liaison with the oncofertility unit Holistic care—medical, psychosocial, housing, transport, education, and career guidance increasing use of telesurvivorship/distant follow-up and shared care
Eligibility criteria	2 years off-treatment; in remission	2 years off-treatment; in remission	Five years from diagnosis; 2 years off-treatment, in remission
Survivors recruited	498	693	1,876
Financial support	—	Limited funding through private donors	Establishment of Holistic Pediatric Foundation in 2010 Dedicated funding for survivors from corporate donors Funds raised in INR/USD (patients supported): 2016-INR 5.1 million; USD 69,622 (51) 2017: INR 7.7 million; USD 103,596 (130) 2018: INR 9.9 million; USD 132,844 (108) 2019: INR 19.7 million; USD 277,606 (192) 2020: INR 14.2 million; USD 193,582 (154)
Support for housing/ accommodation	—	Partial support through 3 HAH NGOs	Reimbursement of housing for those in need Support through 3 HAH NGOs
Educational/ vocational rehabilitation	—	Limited vocational rehabilitation via partner NGOs	Educational scholarships for patients on maintenance and survivors via pediatric foundation, NGOs, and individual donors. Vocational rehabilitation via multiple partner NGOs

Abbreviations: ACT, After Completion Treatment; AYA, Adolescent and Young Adult, HAH, Home Away from Home; INR, Indian rupees; NGO, nongovernmental organizations; USD, US dollars.

performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp, Armonk, NY).

This study was approved by the Institutional Ethics Committee at the Tata Memorial Centre, and waiver of informed patient consent was obtained.

RESULTS

Demographic Profile and Spectrum of Late Effects

From February 5, 1991, to February 4, 2021, 3,067 long-term survivors of childhood cancer were enrolled into the ACT Clinic. A large proportion of survivors use the clinic as their primary point of late effects care, with an average of 400-500 new enrolments annually and 40 follow-up visits/week.

The demographic profile and outcomes of these survivors are detailed in Table 2. The cohort has a median current age of 18 years (range, 3-57 years), with a median follow-up of 11 years (range, 2-46 years). The gender ratio is skewed with 2.5 times more males. The most common diagnoses included Acute Lymphoblastic Leukemia (ALL, 26.5%), Hodgkin Lymphoma (HL, 18.5%), and Wilms' Tumor (8%). More than one third had received chemotherapy and radiation, whereas approximately a fifth received chemotherapy alone or in combination with surgery (Table 2). Overall, half the cohort had received radiation therapy (any site) and 11% had received cranial irradiation (Table 3). The survivors belong to all regions across India; 35% are from Maharashtra state (where the clinic is situated), and

TABLE 2. Demographics and Outcome of Survivors (N = 3,067) Enrolled From February 1991 to February 2021

Characteristic	No.
Age at diagnosis, years, median (range)	6 (0-18)
Duration of follow-up, years, median (range)	11 (2-46)
Current age, years, median (range)	18 (3-57)
Gender ratio	2.5:1
Diagnosis, No. (%)	
ALL	813 (26.5)
HL	567 (18.5)
WT	245 (8)
Ewing sarcoma	204 (6.7)
NHL	199 (6.5)
Germ cell tumor	184 (6)
Rhabdomyosarcoma	160 (5.2)
Neuroblastoma	147 (4.8)
Brain tumor	125 (4.1)
Retinoblastoma	106 (3.5)
Acute myeloid leukemia	79 (2.6)
Hepatoblastoma	55 (1.8)
Osteosarcoma	48 (1.6)
Others	135 (4.2)
Treatment received, No. (%)	
Chemotherapy + radiation	1,217 (39.6)
Chemotherapy alone	605 (19.7)
Surgery + chemotherapy	597 (19.4)
Surgery + chemotherapy + radiation	513 (16.7)
Surgery alone	77 (2.5)
Surgery + radiation	60 (2)
Radiation alone	2 (0.1)

Abbreviations: ALL, acute lymphoblastic leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin Lymphoma; WT, Wilms' Tumor.

the rest come from all parts of India (mainly Northern and Eastern India).

Nearly two thirds (1,914 [62.4%]) of survivors had either no or mild late effects, and 480 (15.6%), 497 (16.2%), and 162 (5.3%) had grades 2, 3, and 4 late effects. Sixty-seven deaths were recorded overall, 53 attributable to recurrence/second neoplasm. Among the common late effects (all grades) in this cohort were chronic viral hepatitis (7.8%); thyroid dysfunction (7.5%); other endocrine issues including growth and hypogonadism (13.6%); abnormal hearing (5.2%); and cardiac (5%), respiratory (6%), and metabolic syndrome (4%; Table 3). Survivors with diagnoses of retinoblastoma, brain tumor, and nasopharyngeal carcinoma had the highest cumulative incidence of late effects grade 3 and above (76%, 56%, and 55% respectively), followed by bone tumors (Ewing sarcoma 41.2% and osteosarcoma 57.5%), Rhabdomyosarcoma (43.7%), HL (15.7%), non-HL (14.5%), and ALL (10.8%).

Transfusion-Transmitted Infections

These were noted in 245 (7.8%), with hepatitis B in 235 (7.5%) and hepatitis C in 26 (0.7%). Of these, 133 did not receive any antiviral treatment and 112 were receiving/had received antivirals in the past. One patient died of chronic liver disease and subsequent hepatocellular carcinoma.

Fertility Outcomes

Sixty-two females and 135 males were documented as married, and four males and three females as divorced. In 35 instances, spouses were unaware of the survivor's previous cancer diagnosis (unrelated to sex of the survivor). Sixty-three (53%) males and seven (16.6%) females were infertile ($P < .001$). Seventy males had offspring—49 normally conceived, 15 after intervention, and six adopted. Thirty-three females had offspring, all normally conceived. None of the offspring has medical concerns, including cancer. In addition, 34 of the unmarried survivors were documented to have hypogonadism (Table 3).

Neurocognition and Psychosocial Issues

One hundred and twenty-six (4.1%) of the cohort were found to have moderate-severe neurocognitive impairment. The prevalence was highest in brain tumors (17.4%), ALL (4.4%), and Hodgkin Lymphoma (3.7%). Age at diagnosis and sex were not significantly associated with neurocognitive impairment. Formal neurocognitive assessment of 261 survivors referred on the basis of clinical concerns and assessed using the Wechsler Intelligence Scale for Children showed moderate-severe intellectual disability in 22 (8.4%), mild intellectual disability in 37 (14.4%), average in 145 (55.5%), borderline in 38 (14.6%), and superior/very superior intelligence in five (1.9%).

Our cohort had a high prevalence of scholastic problems (43%), school dropouts (13%), and other psychosocial issues (overall 57%). Eighty-five (2.7%) of survivors were documented to have either a psychiatric issue or significant psychological issue needing intervention.

Subsequent Neoplasms

There were overall 162 survivors who developed subsequent neoplasms (malignant = 50 and benign = 26) or late recurrences (n = 86) in this cohort. The commonest subsequent malignant neoplasms (SMNs) included papillary carcinoma thyroid (n = 10), Ewing sarcoma (n = 7), and glioblastoma (n = 5); benign neoplasms included benign thyroid nodules (n = 6), fibroadenoma (n = 5), and meningioma (n = 5). The median time to develop SMN was 14 years (range 2-29 years), and late recurrence was 7 years (2-27 years).

Deaths

The documented late mortality in this cohort was 67 (1.92%), 53 deaths because of SMN and relapse, five

TABLE 3. Side Effects by the Decade of Diagnosis of the Survivors

Characteristic	All Survivors (N = 3,067)	1971-1980 (n = 22)	1981-1990 (n = 261)	1991-2000 (n = 574)	2001-2010 (n = 1,341)	2011-2020 (n = 869)	*P*
Duration of follow-up, years, median (range)	11 (2-46)	25 (12- 42)	20 (3-46)	16 (2-33)	12 (3-21)	8 (2-11)	
Current age, years, median (range)	18 (3-57)	30 (16-53)	26 (7-57)	22 (3-45)	18 (4-35)	14 (3-28)	
Gender ratio	2.5:1	2:1	3:1	2.8:1	2.5:1	2.5:1	.13
Lost to follow-up, No. (%)	720 (22.5)	18 (81)	182 (69.7)	323 (56.2)	179 (13.3)	18 (2.1)	< .001
Received radiation (any site), No. (%)	1,787 (58.3)	17 (77.2)	215 (82)	334 (58.1)	807 (60)	414 (47.6)	< .001
Received cranial irradiation, No. (%)	351 (11.4)	11 (50)	93 (35.6)	107 (18.6)	105 (7.8)	35 (4)	< .001
NCI CTCAE grading of late effects[a]							
Grade, No. (%)							
0/1	1,914 (62.4)	8 (36.4)	100 (38.3)	327 (56.9)	815 (59.5)	664 (76.4)	< .001
2	480 (15.6)	2 (9.1)	30 (11.5)	77 (15.5)	242 (18)	129 (14.8)	
3	497 (16.2)	7 (31.8)	94 (36)	123 (19.1)	222 (16.5)	51 (5.8)	
4	162 (5.3)	5 (22.7)	30 (11.5)	42 (7.3)	61 (4.5)	24 (2.7)	
Subsequent neoplasms,[b] No. (%)	76 (2.4)	4 (18)	22 (8.4)	26 (4.5)	20 (1.6)	4 (0.5)	.008
Deaths overall,[b] No. (%)	67 (1.92)	2 (9)	16 (6.1)	25 (4.3)	16 (1.2)	8 (0.9)	< .001
Deaths because of relapse/SMN [b]	53	2	9	20	15	7	
Late effects–related deaths	5	0	4	1	0	0	
Other reasons (accidents/other medical reasons)	9	0	3	4	1	1	
Grade change[c]	230 (7.5)	5 (22.7)	73 (26.8)	92 (16)	48 (3.3)	12 (1.4)	< .001
Prevalence of late effects by organ dysfunction (includes all grades)							
Transfusion-transmitted infections	245 (7.8)	7 (32)	70 (26.7)	82 (14.3)	48 (3.8)	35 (4)	< .001
Hepatitis B	235 (7.5)	7 (32)	67 (25.7)	82 (14.3)	46 (3.4)	33 (3.8)	< .001
Hepatitis C	26 (0.7)	2 (9)	11 (4.2)	4 (0.7)	5 (0.4)	4 (0.5)	< .001
Thyroid dysfunction	229 (7.5)	4 (18)	38 (14.5)	65 (11.3)	99 (7.3)	23 (2.6)	< .001
Other endocrine dysfunction (including short stature)	417 (13.6)	7 (32)	103 (39.4)	125 (21.7)	183 (13.6)	31 (3.6)	< .001
Infertility + hypogonadism	104 (3.3)	4 (18)	45 (17.2)	33 (5.7)	17 (1.2)	5 (0.6)	< .001
Abnormal hearing	158 (5.2)	3 (13.5)	34 (13)	42 (7.3)	71 (5.3)	10 (11.5)	NS
Metabolic syndrome[d]	64 (4.2)	—	—	—	—	—	
Overweight[d]	298 (20)	—	—	—	—	—	
Underweight[d]	405 (27)	—	—	—	—	—	
Cardiac	165 (5.4)	4 (18)	32 (12.2)	76 (13.3)	32 (2.4)	21 (2.4)	< .001
Respiratory	187 (6)	4 (18)	14 (5.3)	79 (13.6)	81 (6)	9 (1.1)	< .001
Renal	25 (0.8)	0	2 (0.8)	2 (0.3)	19 (1.4)	2 (0.2)	NS
Neurocognitive	126 (4.1)	2 (9)	23 (8.8)	50 (8.6)	38 (2.8)	13 (1.5)	< .001

Abbreviations: ACT, After Completion Treatment; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; SMN, second malignant neoplasm.

[a]NCI CTCAE grading: grade 0: Normal; grade 1: Mild symptoms; clinical or diagnostic observations only; intervention not indicated; grade 2: Moderate; minimal, local, or noninvasive intervention indicated; grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL; grade 4: Life-threatening consequences; urgent intervention indicated; grade 5: Death related to AE.

[b]These numbers are subcohorts and are not to be counted separately toward denominator.

[c]Change in grade defined as an increase in severity of late effects on the basis of NCI CTCAE grading from enrollment in ACT Clinic to last follow-up.

[d]Denominator for nutritional assessment = 1,500 (data not available by the decade of diagnosis).

because of other late effects (two cardiomyopathy, one renal failure, one uncontrolled diabetes mellitus, and one complicated pancreatitis), and nine because of unrelated causes. There was a significant decline in late mortality in the most recently treated cohort (Table 3).

Attrition to Follow-Up

Nearly one fourth (22.5%) of the entire cohort is lost to follow-up, with 60% of survivors treated before 2000 being lost to follow-up. Older age of survivors, longer time from diagnosis, and residence outside of Mumbai were significantly associated with attrition to follow-up ($P = .004$, .01, and < 0.001 respectively).

Analysis of Temporal Trends by the Decade of Diagnosis

Table 3 details the profile of late toxicities by the decade of cancer diagnosis and treatment. There was a consistent decrease in the cumulative incidence of grade 2 and higher late effects in subsequent decades, including transfusion-transmitted infections; thyroid and other endocrine dysfunction; cardiac, respiratory, and neurocognitive dysfunction; and subsequent neoplasms and deaths (Table 3). There were a slight improvement in the gender ratio and decreased attrition to follow-up in recently treated survivors.

The updated follow-up of the original cohort of 625 patients confirmed the increase in cumulative incidence and severity of late toxicities with longer follow-up (25 years *v* 11 years). Cardiac late effects and subsequent malignant neoplasms/relapse were significantly increased. Although the absolute numbers of chronic hepatitis B/C and thyroid/endocrine dysfunction increased with increased follow-up, the proportion among patients tested remained constant (Appendix Table A1).

DISCUSSION

From its inception in 1991, the ACT clinic has been focused on service delivery, expanding over the past three decades to offer multidisciplinary care and holistic rehabilitation. An early report from the ACT Clinic (n = 625) was the first of its kind from India and possibly a LMIC. In this cohort, 32% had late effects requiring any form of intervention with growth disturbances (16%), endocrine dysfunction (18%), chronic viral hepatitis (20%), and cardiac toxicity (16%) being issues of concern.[8,9]

In the current, expanded cohort of more than 3,000 survivors, 37.6% had late effects of grade 2 and higher. The gender ratio is skewed with 2.5 times more males, reflecting the gender ratio at initial cancer diagnosis. The most common diagnoses included those with the best long-term survival outcomes—ALL (26.5%), HL (18.5%), and WT (8%). Notably, more than half of the cohort had received radiation therapy (any site) and 11% had received cranial irradiation although there has been a significant reduction in the use of radiation in recent years. Although not analyzed for this article, chemotherapy protocols at our center in the past two decades have incorporated risk stratification and either omitted or reduced the dose of alkylating agents and anthracyclines**.** The late effect profile with reductions in anticancer therapy has shown a decrease in severity, including late mortality.

The two largest reports of outcomes in childhood cancer survivors from other centers in India consist of 300 and 155 survivors.[16,17] In the first report (n = 300, median follow-up 8.5 years), 23% had a minimal disability and 13% had moderate disabilities needing medical attention; 11 relapses, 2 second malignancies, and 5 deaths were reported.[16] The second report (n = 155, median follow-up 8 years, median age 24 years) noted impaired fertility (24.5%), impaired growth pattern (4.5%), endocrine dysfunction (4.5%), and second malignancy (1.2%) to be major concerns.[17] Other studies have focused on specific subsets of survivors.[3]

The spectrum of late effects in India (including at our center) is similar to those reported in the world literature, with certain issues such as transfusion-transmitted viral infections, metabolic syndrome, and psychosocial issues being specific concerns.[3,18] Of note, in our cohort is the large proportion of survivors with neurocognitive and psychosocial issues. Although the conventional risk factors for neurocognitive impairment in survivors of childhood cancer are well recognized, scholastic problems and school dropout in India are multifactorial.[19,20] A controlled comparison with the sibling cohort is essential for a meaningful root-cause analysis and sustainable intervention. Although only 4% of the cohort had metabolic syndrome, this was concerning in view of the young median age of 18 years and 20% prevalence of overweight. Metabolic syndrome and altered body composition are emerging chronic health issues among Indian survivors of childhood cancer.[10,21]

In our cohort, survivors with diagnoses of retinoblastoma, brain tumor, and nasopharyngeal carcinoma had the highest cumulative incidence of late effects grade 3 and above, possibly because of the large proportion of patients who underwent radiation and enucleation (in retinoblastoma) and use of cranial-directed radiotherapy in the others. Similarly, a high proportion of bone tumors underwent surgeries such as amputation and chemotherapy with alkylating agent and anthracyclines. A varied late toxicity profile in survivors of retinoblastoma, including a poorer quality of life, has been documented in other reports from North America and India.[22-24]

The current article reports the late effect profile of an expanded cohort with the longest follow-up from India. Although the median follow-up of the entire cohort is 11 years, the median age of survivors is 18 years; 300 and 600 survivors have been followed up for more than 20 and 15 years, respectively. Moreover, all toxicities are clinically ascertained in line with standard recommendations.

The subcohort of survivors with a relatively long follow-up allows for reporting of outcomes such as subsequent

neoplasms and fertility in our population, and attrition of large numbers of longer-term survivors (up to 60% in those treated before 2000) has led to gaps in the data. Older age of survivors, longer time from diagnosis, long distance, gaps in awareness, financial toxicity, and social stigma are causes of attrition.[18] The recently updated data of our initially published cohort of 625 survivors showed that there was a 62% attrition to follow-up.[9] The remaining cohort had a 66.4% prevalence of late effects requiring intervention, double from 32% at 10 years, including a 6-fold increase in mortality (Appendix Table A1). The cumulative incidence of cardiac and respiratory toxicities as well as subsequent neoplasms showed an increase with a longer duration of follow-up, but transfusion-transmitted infections and thyroid dysfunction remained relatively stable. Notably, more survivors received targeted testing between 2002 and 2021. It could be hypothesized that a large proportion of the lost to follow-up survivors have suffered severe late effects including death, with a small proportion leading completely normal lives, far removed from their history of cancer. These findings are consistent with the most literature and appears to be a universal challenge.[2,25,26] We have tried to tackle this major problem by incorporating counseling regarding the need for continuous follow-up and proactively reaching out by postal letters and telephone calls in the case of missed follow-up appointments. Possibly the most effective strategy in ensuring follow-up has been the establishment of a holistic support model (Table 1), which combines substantial financial assistance for treatment and educational/vocational guidance. The increasing use of telesurvivorship has emerged as a preferred mode of consultation for many survivors who might not have followed up otherwise.[27]

Our analysis found a consistent decrease in the cumulative incidence of severe late effects including mortality in recent decades, as described in other, larger cohorts.[28] In our cohort, however, these findings might be confounded by the shorter duration of follow-up. In a separate analysis, an additional 14 years of follow-up data showed an increase in the cumulative incidence of cardiac late effects and subsequent malignant neoplasms/relapse in the original cohort of 625 patients. Detailed analysis of medical and psychosocial late effects in this cohort has been presented at various conferences and is the subject of a separate manuscript in preparation.[29-36]

With an ever-increasing cohort of childhood cancer survivors and a limited capacity to expand further, we are attempting to decentralize care by developing a strong multicentric network of late effects clinics at our allied centers providing holistic, standardized care. Incorporation of technology to facilitate survivorship care in our cohort of largely adolescent and young adults is another priority. There is a definite need to improve communication, build rapport, and improve education of patients/survivors, families, and health care professionals regarding potential late toxicities. Several research projects at our center attempt to minimize and alleviate late toxicities, especially neurocognitive issues in brain tumors, and azoospermia.[29,37-39]

In conclusion, it is both feasible and crucial to establish and sustain a survivorship program in centers treating children with cancer in LMICs, where the late effects differ from those described in the Western literature. Understanding the unique spectrum of late effects and multifactorial etiology helps ensure holistic and sustainable support. Although survivors of childhood cancer treated on contemporary treatment protocols have a significantly lower side-effect profile, several gaps need to be bridge to ensure the long-term physical and mental health and psychosocial support of childhood cancer survivors.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Long-Term Follow-Up of the Initial Cohort of 625 Survivors

Characteristic	Data Updated 2002[a]	Data Updated 2021
Lost to follow-up, No. (%)	—	390 (62.4%)
Duration of follow-up in years, median (range)	11 (2-29)	25 (16-46)
Current age of alive survivors in years, median (range)	—	31.5 (18-57)

NCI CTCAE Grading of Late Effects[b]	Data Updated 2002,[a] No. (%)	Data Updated 2021, No. (%)	*P*
Grade			
0	284 (46)	47 (20)	< .0001
1	140 (22)	32 (13.6)	.004
2	54 (9)	42 (18)	.0002
3	121 (20)	62 (26.4)	.03
4	21 (3.2)	66 (28)	< .0001
Death[c]	14 (2)	30 (12.7)	< .0001
Cumulative incidence of late effects (includes all grades)			
Transfusion-transmitted infections			NS
Chronic hepatitis B	109 (20)	117 (21.2)	
Chronic hepatitis C	7 (6)	17 (3.8)	
Thyroid dysfunction	74 (49% of tested)	81 (45.7% of tested)	NS
Endocrine dysfunction (including short stature)	111 (18% of tested)	132 (21.1% of tested)	NS
Cardiac	44 (16% of tested)	80 (24.6% of tested)	.008
Respiratory	30 (25.4% of tested)	52 (23% of tested)	NS
Relapse	10 (1.6)	22 (3.5)	.03
Subsequent malignant neoplasm	11 (1.7)	38 (6.1)	.001

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute.

[a]Data extracted from Tonorezos et al.[7]

[b]NCI CTCAE grading: grade 0: normal; grade 1: mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2: Moderate; minimal, local, or noninvasive intervention indicated. Grade 3: Severe or medically significant but not life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Grade 4: Life-threatening consequences; urgent intervention indicated. Grade 5: Death related to AE.

[c]All-cause deaths, including deaths because of grade 4 toxicities and causes unrelated to cancer treatment.

