TITLE PAGE: NEUROCOGNTIVE OUTCOMES IN SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA: EXPERIENCE FROM A TERITARY CARE CENTRE IN INDIA

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Abstract

BACKGROUND: Neurocognitive deficits are an important late effect in survivors of acute lymphoblastic Leukemia(ALL). Data from low middle income countries is scarce and highly influenced by biological and cultural variations. Such data would be useful for highlighting the importance of early intervention in an already disadvantaged population. PROCEDURE: 70 consecutive survivors of childhood ALL were evaluated for neurocognitive deficits by the Indian adaptation of Wechsler Intelligence Scale for Children-Fourth Edition(WISC-INDIA). Prevalence of neurocognitive deficits was calculated based on Full Scale Intelligence Quotient(FSIQ) and scores in discrete domains like Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed were calculated and compared to baseline characteristics, chemotherapy and radiation dose received. RESULTS: The mean FSIQ was 86.1 $\pm$ 20.5, with significant neurocognitive deficit(FSIQ <90) being prevalent in 50%(95% CI 38% to 62%) of the cohort. The proportion of survivors with deficits in individual domains of verbal comprehension, perceptual reasoning, working memory and processing speed were 49%, 50%, 47% and 44% respectively. The odds of having deficits in neurocognitive function was higher when a child belonged to lower socioeconomic strata, had parents with less than primary school education and whose birth order was higher(All $p<0.05$). Age at diagnosis, current age at assessment, receiving lower or higher dose of radiotherapy, high dose methotrexate or cytarabine did not have a direct impact on neurocognitive function. CONCLUSIONS AND RELEVANCE: The current need is to develop country specific neurocognition assessment tools to initiate early screening and develop culturally appropriate preventive and rehabilitative interventions.

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Abbreviation	**Full Form**
ALL	Acute lymphoblastic leukemia
WISC-^{INDIA}	Wechsler Intelligence Scale for Children-Fourth Edition
FSIQ	Full Scale Intelligence Quotient
CNS	Central nervous system
LMIC	Low Middle Income Countries
AIIMS	All India Institute of Medical Sciences
VCI	Verbal Comprehension Index
VC	Vocabulary
CO	Comprehension
WR	Word reasoning
IN	Information
SI	Similarities
PRI	Perceptual Reasoning Index
BD	Block designing
PC	Picture Concepts
MR	Matrix Reasoning
PCm	Picture completion
WMI	Working Memory Index
DS	Digit Span

Abbreviation	Full Form
LN	Letter-number sequencing
AR	Arithmetic
PSI	Processing Speed Index
CD	Coding
SS	Symbol Search
CA	Cancelling
SD	Standard Deviation
IQR	Inter quartile Range
IV	Intravenous
IT	Intrathecal
CRT	Cranial Radiotherapy
TNF	Tumor Necrosis Factor

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PROCEDURE: 70 consecutive survivors of childhood ALL were evaluated for neurocognitive deficits by the Indian adaptation of Wechsler Intelligence Scale for Children-Fourth Edition(WISC-^{INDIA}). Prevalence of neurocognitive deficits was calculated based on Full Scale Intelligence Quotient(FSIQ) and scores in discrete domains like Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed were calculated and compared to baseline characteristics, chemotherapy and radiation dose received.

RESULTS: The mean FSIQ was 86.1 $\pm$ 20.5, with significant neurocognitive deficit(FSIQ <90) being prevalent in 50%(95% CI 38% to 62%) of the cohort. The proportion of survivors with deficits in individual domains of verbal comprehension, perceptual reasoning, working memory and processing speed were 49%, 50%, 47% and 44% respectively. The odds of having deficits in neurocognitive function was higher when a child belonged to lower socioeconomic strata, had parents with less than primary school education and whose birth order was higher(All $p<0.05$). Age at diagnosis, current age at assessment, receiving lower or higher dose of radiotherapy, high dose methotrexate or cytarabine did not have a direct impact on neurocognitive function.

CONCLUSIONS AND RELEVANCE: The current need is to develop country specific neurocognition assessment tools to initiate early screening and develop culturally appropriate preventive and rehabilitative interventions.

INTRODUCTION:

Acute lymphoblastic leukemia(ALL), being the most prevalent malignancy of childhood, has seen a barrage of treatment advances in the past few years[1]. Better management has lead to improved survival, which in turn has lead to an increased population of survivors of ALL. India too has seen a fair share of improvement in survival of children with ALL, ranging between 41-70%[2]. In the current era , the treatment of ALL is most often done by chemotherapy. Cranial irradiation is almost obsolete, restricted only to patients presenting with central nervous system(CNS) positive disease. Targeted therapy/bone marrow transplantation are considered only in certain high risk groups. Pediatric oncologists all over the world are approaching a more holistic approach to cancer care, of which survivorship is an important component. Late effects are increasingly seen in survivors of ALL, to the tune of almost 75%[3]. Among late effects, neurocognitive deficits are extremely worrisome and significantly affect the quality of life of the survivor and the family. Past studies which have assessed neurocognitive deficits in survivors of acute leukemia have found its prevalence

to be around 38 to 58%[4]. There are significant racial and ethnic variations in the biology of ALL which may be translated into survivorship, an area that has not been explored adequately, particularly in Low Middle Income Countries(LMIC). Hence we conducted a study to evaluate the prevalence and spectrum of neurocognitive deficits in survivors of childhood ALL, aged 6 to 17 years, who have completed treatment with documented remission of at-least 2 years and to determine various factors associated with these deficits.

METHODOLOGY

Participants: ALL survivors attending the Pediatric Cancer Survivorship Clinic (PCSC) were enrolled after a written informed consent. The study was performed between July 2016 to November 2017. A total of 70 survivors of ALL were recruited. The institutional review board of All India Institute of Medical Sciences(AIIMS), approved the study protocol. Eligibility criteria included survivors of ALL, aged 6-17 years who had completed treatment and had a documented remission of atleast 2 years. Exclusion criteria included history of any central nervous system(CNS) or sensory-motor deficits during treatment, concurrent neurological or psychiatric disorder not primarily attributed to ALL or any previous genetic diagnosis with known association with neurocognitive impairment(eg., Down syndrome).

Definitions

1. **Treatment completion:** Completion of maintenance phase of treatment protocol.
2. **Childhood Cancer Survivor:** One who has completed treatment of childhood cancer and is in continued remission for at-least 2 years post treatment completion[5,6].
3. **Late Effects:** Late effects are defined as any physical or psychological outcome that develops or persists after treatment is completed[5,6].
4. **Neurocognitive Deficits:** Encompasses the group of disorders in which the primary clinical deficit is in cognitive function and that are acquired rather than developmental[7].

Sample size: Based on previous studies[4], the prevalence of neurocognitive deficits in ALL survivors was taken as 58.9% and the sample size was calculated with a relative precision of 20% to be 70.

Procedures: Children who met the inclusion criteria, and whose parents/guardians provided a written informed consent, were included in the study. Each participant underwent a basic anthropometric evaluation and medical assessment. Complete demographic details including age, sex, current address, family type, birth order, parental education levels were documented. Socioeconomic stratification was done based on the modified kuppuswamy scale, which is based on education, occupation and income of the head of the family[8]. Exposure data, including chemotherapy used(with cumulative doses), radiation received and surgical procedures done, was retrieved from the participants medical records stored in their clinic files. Information was collected on a detailed proforma.

Neurocognitive Evaluation:

Neurocognitive testing was conducted in dedicated evaluation rooms, where the testing enviornment was free of distractions and both the examiner and examinee were comfortable. The Indian adaptation of Wechsler Intelligence Scale for Children-Fourth Edition(WISC-IV$^{\text{INDIA}}$) was used for the assessment of neurocognitive deficits[9]. This is a valid, reliable and individually administered comprehensive clinical instrument for assessing the cognitive ability of children aged between 6 years 0 months to 16 years 11 months and is available commercially. WISC-IV$^{\text{INDIA}}$ assesses four primary domains of cognition, using 15 subtests, which represent a childs abilities in more discrete cognitive domains. The scores of the four domains are integrated to generate the Full Scale Intelligence Quotient(FSIQ), that represents a child's general intellectual ability.

Before the start of study, training about the WISC-IV$^{\text{INDIA}}$ scale was obtained from the Child Psychologist, who supervised the assessments and was a co-investigator. During the study, one fifth of the assessments were randomly cross-checked by the Psychologist.

As per WISC-IV$^{\text{INDIA}}$ the first cognitive domain assessed is the Verbal Comprehension Index(VCI), using subtests on Vocabulary(VC), Comprehension(CO), Word reasoning(WR), General knowledge(Information,

IN) and finding similarities(SI). The second domain assessed is Perceptual Reasoning, which is the ability of a person to draw upon visual-motor and visual-spatial skills, organize their thoughts, create solutions, and then test them. The Perceptual Reasoning Index(PRI) is assessed by Block designing(BD), Picture conceptualization(Picture concepts, PC), Matrix reasoning(MR) and Picture completion(PCm). The third domain tested is the Working Memory Index(WMI). Participants are assessed on their ability to repeat numbers in order(Digit Span, DS), read a sequence of numbers and letters(Letter-number sequencing, LN) and mentally solve arithmetic problems(Arithmetic, AR). The fourth and final domain evaluated is processing speed which tests the childs ability to focus their attention, quickly scan and discriminate between objects and put them in order sequentially. The Processing Speed Index(PSI) is calculated by drawing symbols in corresponding shapes(Coding, CD), searching for symbols(Symbol Search, SS) and marking and cancelling targeted pictures(Cancelling, CA).

There are 10 primary and 5 supplemental subtests. The primary sub tests are vocabulary, comprehension, finding similarities, block designing, picture conceptualisation, matrix reasoning, digit span, letter-number sequencing, coding, and symbol search(10 total). Two subtests were administered to obtain each of the primary index scores. FSIQ was derived from 8 of the 10 primary subtests. Acceptable substitutions as per WISC-IV$^{\text{INDIA}}$ manual were taken. Hence, for the purpose of this study, subtests selected for assessment of FSIQ were directed at assessing comprehension, similarities, picture completion and picture conceptualisation, digit span, arithmetic, coding and cancellation. Each subtest provided a 'Raw Score'. These 'Raw Scores' were converted into a 'Scaled Score' using the WISC-IV$^{\text{INDIA}}$ manual based on the exact chronological age, using the Date of Birth or age in completed years as remembered by the guardians. Each primary index domain was derived from the sum of scaled scores.

The FSIQ was obtained from the four primary index scores. The prevalence of neurocognitive deficits was calculated based on this FSIQ, with presence of neurocognitive deficits taken at a FSIQ of <90. Spectrum of deficits was analysed by calculating the prevalence of deficits in each of the 4 primary index scores. Any score less than 90 was considered as a deficit in that particular domain. A structured record form was used to document all assessment details, scores and calculations.

Statistical Analysis: The data was analysed using with STATA 14.2 software. Categorical data was tested by the Chi-square or Fischer extract test and presented as percentage or proportion. Continuous data, which was normally distributed, was presented as Mean ± Standard Deviation(Mean ± SD) and the data which is not normally distributed is presented as Median with corresponding Inter-Quartile Range(Median + IQR). The prevalence of neurocognitive deficits in the sample population was calculated in percentage, including complete and individual demain deficits. The various factors associated with neurocognitive deficits in sample population was also assessed using multiple logistic regression analysis. Odds ratio was calculated along with 95% confidence interval. In all analysis, p value <0.05 was considered to represent a statistically significant difference.

RESULTS

Baseline characteristics:

Baseline characteristics are provided in **Table 1** . Treatment was instituted as per chemotherapy protocols of the intitute at that period of time which were differed among patients. Details of relevant cumulative drugs are provided. Radiotherapy was received by all patients as per protocol(1260cGy for prophylaxis and 1800cGy to treat CNS positive leukemia). As per treatment protocol at the time, our cohort received either Protocol A or B. Protocol B included high dose methothrexate, triple IT and a higher dose of dexamethasone and cyatarabine as compared to protocol A. Our cohort averaged a total of 27.1 months of delay in schooling.

Neurocognitive outcomes (Table 2):

The primary outcome assessed in this study was the full scale intelligence quotient (FSIQ). The mean FSIQ of the entire sample population was 86.1 ± 20.5. The prevalence(95% confidence interval) of significant neurocognitive deficits(FSIQ <90) in the sample population was 50%(38% - 62%), with 18 children having

extremely low FSIQ(25.7%), 7 with borderline FSIQ (10.0%) and 10 with low average FSIQ(14.3%).

Individual domains (Table 3):

Using the WSIC-IV^{INDIA}, various domains of neurocognition was assessed. The first domain is verbal comprehension, assessed by the Verbal Comprehension Index. The mean VCI of the entire sample population was 88.4(SD 21.6), with 34(49%) children showing a significant deficit in this domain(VCI score < 90).

The second domain was perceptual reasoning, whach was tested by the Perceptual Reasoning Index and included assessment of block designing, picture conceptualization, matrix reasoning and picture completion abilities. The PRI was 89.0(SD 18.0) with 35(50%) of the population having a score of <90.

The working memory of the entire sample population was the third domain assessed. The mean WMI calculated was 87.5(SD 21.0) and 33(47%) children were found to have a significant deficit of WMI(< 90).

The fourth and final domain evaluated was the processing speed ability of an individual by the processing speed index. The mean PSI of the entire sample population was 90.3(SD 19.0) with 3(44%) children having clinically significant neurocognitive deficit.

Patient related risk factors associated with poor neurocognitive domains (Table 4):

Univariate analysis with multivariate logistic regression was used to assess various risk factors associated with significant neurocognitive deficits (FSIQ<90). The odds of having deficits in neurocognitive function was 5.7 times when a child belonged to lower socioeconomic strata as compared to a child belonging to middle socioeconomic strata (p value=0.004). Parental education had a significant association with adverse neurocognitive deficit with odds being higher when parents were only educated till primary school(4.3 to 4.6 times higher when the father or mother was educated up to primary school respectively). Children whose birth order was 3 or more had a higher probability of having deficits in neurocognitive function(20.1 times higher, p value=0.005). Other factors including gender, age at assessment, age at diagnosis/initiation of treatment and family type did not show any significant association with poorer neurocognitive scores.

Disease and treatment related risk factors associated with poor neurocognitive domains (Table 4):

Age at diagnosis/initiation of therapy did not affect the neurocognitive scores. The entire cohort of patients received either prophylactic or therapeutic cranial radiotherapy(RT). The presence of CNS disease would entail receiving higher dose of RT to the neuralaxis. Receiving higher doses of RT to the neuralaxis was also not associated with poorer FSIQs. Chemotherapy protocol received did not have a directder age at assessment was associated impact on neurocognitive function. Giving higher doses of intravenous methotrexate or cytarabine or using triple IT over IT methotrexate was not associated with increased neurocognitive deficits(OR: 1.0 , 95% CI 0.3-3.5, p 1.000).

Individual cognitive domains in relation to patient and treatment related risk factors (Table 5):

Older age at diagnosis was associated with significantly improved working memory scores. Median age at diagnosis or age at assessment was similar in all other major domains of neurocognition. These scores were also no different between the two genders, type of radiation received or type of chemotherapy used.

DISCUSSION

One of the main challenges after curative treatment of childhood cancer is maintaining an effective follow up to assess various health related complications. There are a wide range of late effects as a result of cancer and its therapeutic exposure. Studies have shown that the cumulative number of health conditions in survivors of ALL are actually twice that identified among matched controls, particulary cardiovascular, endocrine, reproductive and neurological sequelae[10]. At a mean duration of around 5 years from diagnosis, 50% of our cohort of ALL survivors showed significant disturbance in neurocognitive function. Around 75% of our cohort showed a deficit in atleast one domain of neurocognition, which includes verbal comprehension, working

memory, processing speed and perceptual reasoning. This is comparable to a large series of adult survivors of ALL, where neurocognitive impairment ranged between 28.6% for self-reported behavior problems to 58.9% for direct assessment of executive function[4]. The mean FSIQ of ALL survivors from developed countries are almost 20-30 points higher than in our cohort[11,12]. This could be due to regional variation in IQ and socioeconomic status between the two cohorts. However it also signifies the greater need to implement more stringent long term follow up guidelines in LMICs as the baseline prevalence of neurocognitive impairment is high.

Data on neurocognitive outcome in survivors of ALL in LMICs is scarce. According to a review of neurocognitive impairment in Asian Cancer survivors, mild-to-moderate impairment was reported in 10.0–42.8% of survivors[13]. A large series of cancer survivors from India, showed scholastic problems and psychosocial problems in around 43% and 57% of the cohort, respectively[14]. Racial, regional and ethnic variations of cancer and its treatment are known, which increases the burden of chronic health condition in this growing survivor population in LMICs. Hence, the importance of country specific databases of childhood cancer survivors.

As early as 1988, neurobehavioural effect of CRT in survivors of ALL have been demonstrated[15]. These late effects include deficits in attention, memory, processing speed, and visual spatial skills[16]. Demyelination with loss of white matter, microvascular damage, loss of neuronal precursors in hippocampus, basal ganglia and thalamus are all proposed mechanisms for long term radiation induced cognitive decline[17]. This neurocognitive morbidity in survivors of childhood ALL has led to the phasing out of radiation, almost completely from the management of ALL[18,19]. Acute changes in the brain occurring during chemotherapy are also associated with long term neuro behavioural problems[20]. Despite elimination of CRT, modern treatment protocols including high dose methotrexate and IT methotrexate, have been implicated in long term problems in memory, executive function, attention and processing speed[4,21,22]. Methotrexate depletes the folate pool which in turn depletes the availability of methyl-groups and produces an excess of homocysteine and alternative one-carbon sources such as choline and betaine. This leads to an impairment in myelin formation and stabilisation and is a likely explanation for methotrexate induced long lasting neurodevelopmental impairment[23]. Higher plasma methotrexate levels have been shown to be associated with poorer executive function scores[4]. In one study methotrexate decreased the processing speed by 3% for each 1g/m^{2}of methotrexate[4]. A study comparing IT methotrexate with triple IT revealed minor reduction in processing speed in survivors of ALL. CRT, high dose methotrexate and IT therapy have a neurotoxic effect in the early course of therapy. As time passes neurocognitive problems are a result of other therapies like glucocorticoids. The cerebellum and hippocampi have higher number of glucocorticoid receptors and are more affected by exposure to prolonged and high doses of steroids[24]. Comparisons between different glucocorticoids have also been made. Neurocognitive outcome measures evaluated in survivors receiving dexamethasone or prednisolone during induction of ALL, found no difference in outcome measures in either group[25]. Even though almost half of our cohort had neurocognitive dysfunction, the scores were not different in groups of patients receiveing higher dose of CRT compared to lower doses(24Gy vs 18Gy). Higher dose of methotrexate or use of IT methotrexate so did not appear to have adverse effect on neurocognition in our group of survivors. Other factors that can be evaluated to assess the risk of neurotoxicity include markers of oxidative stress[26], cytokines like tumor necrosis factor(TNF) alpha and interleukins[27] and cerebrospinal fluid biomarkers[28].

Neurocognitive dysfunction is seen to be more significant as age increases[29]. Attention problems detected at the end of therapy in survivors of ALL predicted decreased academic performance 2 years later, especially in females and children who had a younger age at diagnosis[30]. It is also believed that patients diagnosed at a younger age and those who received CRT, perform poorly in neurocognitive domains[13,16]. A younger age at diagnosis correlated with poor working memory scores in our cohort. Other domains were not affected by either the age at diagnosis or assessment. Nevertheless, assessment of neurocognition in survivors of ALL should start at a younger age, especially in children in LMICs, where focus is more on survival than survivorship, to allow them to reach their full potential at school and in the workplace.

Additional factors which put a survivor at increased risk of neurocognitive impairment, like polymorphisms in genes related to neurodevelopment, genes affecting the folate pathway and genes that regulate oxidative

stress, have been studied[31]. This can not only help us in stratifying patients according to their genetic risk but also help in tailoring treatment and prophylaxis early in development[32]. Since regional variations affect the genetic makeup of an individual, country specific multicentre collaborative studies are in much need.

There is limited research examining how a childs neurocognitive function following treatment for cancer is associated with parenting factors. A recent study reported that parents respond to child executive function difficulties with greater over protection. Greater years of maternal education were related to less parental perceptions of child vulnerability and less over protection[33]. A univariate analysis in our cohort, showed a significantly lower Intelligence quotient(IQ) in survivors whos' parents had fewer years of education. Other factors like lower socioeconomic status and increased birth order are also associated with lower IQ scores. These are predictable and understandable findings and may also be seen in children who are not cancer survivors. However, since other factors including radiation dose, intensity of chemotherapy or age at primary diagnosis did not alter outcome, focus of neurocognitive behavioural assessment and intervention should be more focussed towards this more vulnerable group of children and adolescents to mitigate the impact of therapy on neurocognitive outcomes.

Poor neurocognition in ALL survivors, has been associated with a marked decrease in quality of life due to increased chronic health morbidities[34]. Survivors of ALL have been believed to perform poorly in school because of probable dysfunction in executive function abilities[(4(p20)]. Compared to their siblings, they have greater degrees of inattention-hyperactivity, anxiety, depression, social withdrawal and learning problems. Adolescent survivors with neurocognitive impairment are also less likely to graduate from college than survivors without any impairment[30]. The St Judes Lifetime Cohort study concluded that though survivors of ALL had significant neurocognitive impairment, overall their educational attainment and employment status was similar to controls[4]. Delay in schooling is a major concern in survivors of ALL from India. Our cohort showed an average of 27 months of delay in schooling despite our best efforts. LMICs, which have their own cohort of young survivors, with poorer overall exposure to basic education, must focus on routine longitudinal screening in childhood survivors of ALL, optimizing their educational, vocational, and social outcomes based on local, regional and cultural practices.

Following a good assessment, survivors of ALL with neurocognitive impairment, should should be taught deficit specific compensatory interventions. This may be a computerised, home, school or even community based training[31]. Pharmacological agents have also been studied. Methylphenidate resulted in a statistically significant improvement in measures related to attention[35]. Future research should focus on interventions to improve neurocognition in ALL survivors.

Several limitations should be considered in interpretation of these results. Firstly, this was a cross sectional study with a small sample size restricted by geographical coverage. Secondly baseline neurocognitive functions of these ALL survivors were not known and there was no healthy control group for comparison. Assessment at time of initiation of treatment may have yieldied falsely low scores associated with anxiety and stress at diagnosis. Thirdly, due to a lack of region specific assessment tools for neurocognitive function, we had to use region specific adaptations of the assessment tool which allowed certain substitutions. Limitations notwithstanding, comparisons were made across treatment groups and patients with or without significant neurocognitive impairment. In addition, the primary focus of this study was to assess the neurocognitive impairment in a group of survivors from a LMIC where baseline educational and vocational opportuinites are challenging even for children without cancer. To the best of our knowledge this was the first study in India, a LMIC, in which WISC-IV scale was used for the assessment of neurocognitive functions in the survivors of childhood ALL. We looked extensively into various factors associated with neurocognitive deficits including host, disease and treatment related factors.

In conclusion, data on neurocognitive outcomes in survivors of ALL are extremely scarce, this being particularly true for our country. Ethnic, geographic and genetic variations predispose survivors differently to adverse chronic neurological toxicities. This can explain the difference in prevalence, severity, and presentation of neurocognitive impairment in survivors of ALL in LMICs. More data from LMICs are needed to assess the time to initiate screening and ways to identify potentially remediable risk factors which in turn

will enable us to develop culturally appropriate preventive and rehabilitative interventions.

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Vishwa CR: Data collection and analysis, writing-original draft. **Gargi Das:** Statistical analysis and writing the final draft. **Rachna Seth:** Planning the study, supervision, writing the final draft and data analysis. **Savita Sapra:** Planning the study, neurocognitive assessment on children, data analysis, editing final manuscript. **Prasanth Sri:** Data analysis and editing the final draft. **Jagdish Prasad Meena, Aditya Kumar Gupta:**Supervision, editing the final draft. **Vishnu Sreenivas:** Data analysis.

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TABLES

TABLE 1 Baseline characteristics of the population

Characteristic
Patient related characteristics
Mean Age (± SD)
Mean duration between diagnosis and enrolment (± SD)
Age distribution 6-9 years 10-13 years 14-17 years
Gender Male Female
Socioeconomic strata Upper Strata Middle Strata Lower Strata
Parental education <Primary school education >Primary school education
Birth order <=2 >2
Family Type Nuclear Multi Generational
Disease and Treatment Related
CNS disease at diagnosis Positive Negative
Radiation received Therapeutic (1800 cGy) Prophylactic (1260 cGy)
Chemotherapy what is protocol A and B Protocol A: IV Methotrexate at 0 mg/m^2 Intrathecal (IT) methotrexate o

TABLE 2 FSIQ distribution in the sample population

FSIQ	Class	Number (%)
<70	Extremely Low	18 (26)

FSIQ	Class	Number (%)
70-79	Borderline	7 (10)
80-89	Low Average	10 (14)
90-109	Average	26 (37)
110-119	High Average	5 (7)
120-129	Superior	3 (4)
>129	Very Superior	1 (2)

TABLE 3 Prevalence of significant deficit in various individual domains

Primary Index score	Number of children with significant deficit (Prevalence in %)	95% CI	Mean +/- SD
Verbal comprehension VCI	34 (49)	37%-60%	88.4 +/- 21.6
Perceptual Reasoning PRI	35 (50)	38%-62%	89.0 +/- 18.0
Working Memory WMI	33 (47)	35%-59%	87.5 +/- 21.0
Processing speed PSI	31 (44)	32%-56%	90.3 +/- 19.0

TABLE 4: Risk factors associated with significant neurocognitive deficit

Character	FSIQ	FSIQ	FSIQ	FSIQ
	Normal(n=35)	Deficiency(n=35)	Odds Ratio (95% CI)	p value
Gender Male, N (%) Female, N (%)	25 (71) 10 (29)	29 (83) 6 (17)	1.9 (0.6-6.1)	0.259
Socioeconomic status Upper Class, N (%) Middle Class, N (%) Lower Class, N (%)	8 (23) 21 (60) 6 (17)	6 (17) 11 (31) 18 (52)	5.7(1.8-18.6)	0.004
Maternal education <=Primary, N (%) >Primary, N (%)	6 (17) 29 (83)	17 (49) 18 (51)	4.6(1.5-13.7)	0.007
Paternal education <=Primary, N (%) >Primary, N (%)	3 (9) 32 (91)	10 (28) 25 (72)	4.3(1.1-17.2)	0.041
Birth Order 1-2, N (%) 3 or more, N (%)	34 (97) 1 (3)	22 (63) 13 (37)	20.1(2.5-164.6)	0.005
Family type Multi Generational. N (%) Nuclear, N (%)	19 (54) 16 (46)	21 (60) 14 (40)	1.3 (0.5-3.3)	0.629

Character	FSIQ	FSIQ	FSIQ	FSIQ
Age at assessment <10 years, N (%) >=10 years, N (%)	18 (51) 17 (49)	16 (46) 19 (54)	1.3 (0.49-3.22)	0.632
Age at diagnosis <4 years, N (%) >=4 years, N (%)	13 (37) 22 (63)	12 (34) 23 (66)	0.8 (0.33-2.34)	0.803
Chemotherapy Protocol A, N (%) Protocol B, N (%)	29 (83) 6 (17)	29 (83) 6 (17)	1.0 (0.3-3.5)	1.000
Radiotherapy 1260 cGy, N (%) 1800 cGy, N (%)	32 (91) 3 (9)	30 (89) 5 (11)	1.8(0.4-8.1)	0.457

Risk Factor	Risk Factor	VCI	VCI	VCI	PSI	PSI	PS
		<90	**>=90**	**P**	**<90**	**>=90**	**P**
Age in months at Diagnosis	Median age (IQR)	55 (23-155)	62 (16-137)	0.18	68 (29-155)	58 (16-131)	0.3
Age in months at assessment	Median age (IQR)	122 (72-203)	115 (63-196)	0.19	120 (72-196)	121 (63-203)	0.0
Gender	Male, N (%)	26 (76)	28 (78)	1.00	26 (84)	28 (72)	0.2
	Female, N (%)	8 (24)	8 (22)		5 (16)	11 (28)	
Radiotherapy	1280 cGy, N (%)	29 (85)	33 (92)	0.47	26 (84)	36 (93)	0.4
	1800 cGy, N (%)	5 (15)	3 (8)		5 (16)	3 (7)	
Chemotherapy	Protocol A, N (%)	29 (85)	29 (80)	0.75	25 (81)	33 (85)	0.7
	Protocol B, N (%)	5 (15)	7 (20)		6 (19)	6 (15)	

TABLE 5 Risk factors associated with individual deficits in the neurocognitive domain

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Table 5 Table 5- Risk factors associated with individual deficits in the neurocognitive domain .docx available at https://authorea.com/users/416997/articles/524259-title-page-neurocogntive-outcomes-in-survivors-of-childhood-acute-lymphoblastic-leukemia-experience-from-a-teritary-care-centre-in-india