

A Study of Clinico-Pathological Profile and Correlation of Outcome with Risk groups of Pediatric Patients with Acute Lymphoblastic Leukemia at a Tertiary Care Centre in North East India

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Abstract

Introduction: Outcome data on Acute Lymphoblastic Leukemia (ALL) treatment remain scarce in developing nations. This retrospective study from the Tata Memorial Centre, Northeast India, aimed to explore the clinical and pathological profiles and to correlate the outcome with risk groups in pediatric patients of ALL in this region. **Materials and Methods:** A retrospective analysis of 418 children newly diagnosed with ALL between May 2015 and April 2020 treated with ALL-IC BFM 2002 protocol was performed. **Results:** Mean age was 7.09 years and median age was 6 years. Most patients were of the Intermediate Risk group. 93 (22.25%) patients had relapse. 72 (17.22%) patients died. After a median observation period of 61 months, the 5-year Event Free Survival (EFS) and Overall Survival (OS) were 69.5% and 72.3% for all patients respectively. Patients in the age group of 1-5 years had significantly better EFS and OS (74.6% and 82.2%, respectively) than in those of ≥ 6 years (62.7% and 69.8%) ($P=0.032$ and $P=0.043$ respectively). Patients with B-ALL had significantly better EFS and OS (72.6% and 75.8%, respectively) than those with T-ALL (57.8% and 59.1%) ($P=0.011$ and $P=0.021$, respectively). Patients who had initial leukocyte counts of $<20 \times 10^9/L$ had better EFS and OS (78.4% and 85.5% vs 56.6% and 64.8%) ($P=0.002$ and $P=0.012$, respectively). Children with a good response to prednisone on day 8 achieved higher EFS and OS (77.7% and 83.7% vs 29.5% and 36.4%) ($P=0.000$ and $P=0.012$). The 5-year EFS and OS were 76.1% and 85.9% for the Standard Risk group, 70.3% and 78.6% for the Intermediate Risk group, and 50.2% and 57.4% for the High Risk group ($P=0.001$ and $P=0.032$, respectively). There was no significant association between sex and survival rates ($P=0.731$). **Conclusion:** The study demonstrates that, with proper risk stratification and corresponding treatment modifications, it is feasible to administer an effective regimen in India and to achieve satisfactory event-free and overall survival outcomes.

Keywords: Acute lymphoblastic leukemia- risk groups- outcome

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Introduction

Acute lymphoblastic leukemia (ALL) is the commonest pediatric malignancy, representing 75-80% of pediatric leukemia. It accounts for 25-30% of all childhood cancers. The age-adjusted incidence rate in the United States is 1.38 per 100,000 population per year [1]. Indian incidence varies with region and age-adjusted rates of up to 101.4 per million and 62.3 per million for boys

and girls, respectively, have been reported [2, 3]. ALL is slightly more common in boys, with peak incidence in 2-5 years. T-ALL constitutes about 15-20% of pediatric ALL; though, in India, a higher proportion of T-ALL (20-50%) has been reported [3].

The survival rate of children with ALL has improved dramatically owing to better understanding of pathogenesis

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and molecular genetics, adoption of risk-stratified therapy and availability of newer therapeutic agents. The five-year overall survival (OS) rate for children has improved to 89% [4]. In India, OS has been estimated at 45-81% [5].

Aims and objectives

The aim of this study was to describe the clinical and pathological profiles of pediatric patients with Acute Lymphoblastic Leukaemia and to correlate outcome with various risk groups.

Materials and Methods

This study was designed as a retrospective study. Children who presented and underwent treatment at the Medical and Pediatric Oncology department of our centre, diagnosed between May 2015 and April 2020 were analysed retrospectively. The study received the institutional ethics committee approval.

Inclusion criteria

Patients up to 18 years of age, attending Tata Memorial Centre-BBCI with a diagnosis of de novo Acute Lymphoblastic Leukemia proven by flowcytometry of blood or bone marrow aspirate or Immunohistochemistry on bone marrow biopsy were included in the study.

Exclusion criteria

Patients who were more than 18 years of age, who did not have documented evidence of antigen expression diagnostic for ALL, those with subtypes of Acute Leukemia other than ALL, and those whose complete treatment and follow-up details were not available were excluded from the analysis.

Treatment Protocol

The treatment protocol was the ALL IC-BFM 2002 protocol. Prednisone response (PR) was determined by absolute blast count in peripheral blood on day 8, after 7 days of prednisone and one dose of intrathecal methotrexate (MTX) on day 1. Prednisone poor response (PPR) was defined as $\geq 1 \times 10^9/L$ blasts, and prednisone good response (PGR) was defined as less than $1 \times 10^9/L$ blasts. Patients were stratified into 3 risk groups according to the following criteria: (1) Standard Risk (SR) defined as PGR, age 1 year to younger than 6 years, initial WBC less than $20 \times 10^9/L$, and M1 (<5% blasts) or M2 ($\geq 5\%$ to <25% blasts) marrow on day 15, and M1 marrow on day 33 (all criteria must be fulfilled); (2) Intermediate Risk (IR), defined as PGR, age younger than 1 year or age 6 years or older, and/or $WBC \geq 20 \times 10^9/L$ and M1 or M2 marrow on day 15 and M1 marrow on day 33, or SR criteria but M3 ($\geq 25\%$ blasts) marrow on day 15 and M1 marrow on day 33 (3) High Risk (HR), defined as at least one of the following: PPR, t (9;22), t (4;11), IR and M3 marrow on day 15, M2 or M3 marrow on day 33; or SR with M3 marrow on day 15 and M2/M3 marrow on day 33; or SR with M1/M2 marrow on day 15 and M2/M3 marrow on day 33. The treatment plan was administered as described in the paper by Stary et al [6].

Event was defined as a relapse of leukemia or death due to any cause. Event-free survival (EFS) was calculated from the date of initiation of treatment to the date of relapse, death or last follow-up. Overall survival (OS) was defined as the time from initiation of treatment to death or the date of last follow-up. Disease and patient characteristics were calculated in percentage. The statistical analysis of the variables of interest was carried out in SPSS v.25 (IBM Corporation, Armonk, NY, USA). The Kaplan–Meier method was used to evaluate event-free survival (EFS) and overall survival (OS), and the log-rank test was used to make comparisons. The threshold for statistical significance (p) was set at $p < 0.05$.

Results

Patients' characteristics

A total of 459 patients of ALL were registered at our institute during the study period between May 2015 and April 2020. Out of 459 cases, 418 children were found to be eligible for the study. Most of the ineligible patients were those who abandoned treatment and were lost to follow-up after the first visit.

In this present study, the mean age was 7.09 ± 0.7 years and the median age was 6 years (Q1=4.3 years, Q3=8.5 years). 196 (46.89%) patients were in the age group of 1-5 years and 222 (53.11 %) patients were in

Table 1. Patient Characteristics

Characteristics	Number	Percentage
Age		
1-5	196	46.89
≥ 6	222	53.11
Gender		
Male	250	59.81
Female	168	40.19
Type		
B	342	81.82
T	76	18.18
Genetic alterations included in High Risk group#		
Absent	396	94.74
Present	22	5.26
TLC		
$< 20 \times 10^9/L$	204	48.8
$\geq 20 \times 10^9/L$	214	51.2
CNS		
Not involved	402	96.17
Involved	16	3.83
Day 8 Prednisone response		
Good	351	83.97
Poor	67	16.03
Risk		
Standard	128	30.62
Intermediate	197	47.13
High	93	22.25

#Genetic alterations included in High Risk group of ALL-IC BFM2002 protocol are translocations t (9;22) and t (4;11)

the age group of ≥ 6 years (Table 1). There were 250 (59.81%) male and 168 (40.19%) female patients. Immunophenotype data of the patients were as following: 342 (81.82%) were B ALL and 76 (18.18%) were T ALL. Cytogenetic analysis by karyotype revealed euploidy in 53% of patients, hyperdiploidy in 31% of patients, hypodiploidy in 3% of patients, pseudodiploidy in 1% of patients; there was culture failure in 12% of patients. Cytogenetic analysis by fluorescent in situ hybridization (FISH) revealed t (12;21), t (1;19), t (9;22), and t (4; 11) translocations in 52 (12.44%), 40 (9.57%), 18 (4.31%) and 4 (0.95%) patients respectively. The only genetic alterations included in the High Risk group of ALL-IC BFM 2002 protocol are the translocations t (9;22) and t (4;11), which together were present in 22 (5.26 %) patients. 204 (48.80%) patients had a Total Leucocyte count (TLC) $< 20 \times 10^9 /L$ and 214 (51.20%) patients had a TLC $\geq 20 \times 10^9 /L$ count at presentation. The minimum TLC was $1.14 \times 10^9/L$ and the maximum TLC was $939.82 \times 10^9/L$. The median TLC was $22 \times 10^9/L$ (Q1= $11.57 \times 10^9/L$, Q3= $480.91 \times 10^9/L$). Involvement of the central nervous system (CNS) at presentation was observed in 16 (3.83%) patients. Day 8 prednisone response was good in 351 (83.97%) patients and poor in 67 (16.03%) patients. According to the ALL IC-BFM 2002 risk stratification, 128 (30.62%) patients were of Standard risk (SR), 197 (47.13%) were of Intermediate risk (IR), and 93 (22.25%) were of High Risk (HR) Group. 93 (22.25%) patients had relapse. 72 (17.22%) patients died due to infections or relapse.

Survival

After a median observation period of 61 months (Q1=32months, Q3=85.5 months), the 5-year EFS

and OS were 69.5% and 72.3 % for all patients. The survival analysis of prognostic variables was also done (Table 2). The EFS at 5 years for patients 1-5 years old was significantly higher than those aged ≥ 6 years old (74.6% vs 62.7%) (P=0.032). The OS at 5 years for patients 1-5 years old was significantly higher than that of those aged ≥ 6 years old (82.2 % vs 69.8%) (P=0.043). The EFS at 5 years for patients with B ALL was significantly higher than those with T ALL (72.6% vs 57.8 %) (P=0.011). The OS at 5 years for patients with B ALL was significantly higher than those with T ALL (75.8% vs 59.1%) (P=0.021). The EFS of the patients with absence of genetic alterations of the HR group was significantly better than in those with their presence (79.9% vs 53.5%) (P=0.001). The OS of the patients with the absence of genetic alterations of the HR group was significantly better than in those with their presence (86.7% vs 66.2%) (P=0.033). Patients who had initial leukocyte counts of $< 20 \times 10^9/L$ had significantly better EFS than children with initial leukocyte counts $\geq 20 \times 10^9 /L$ (78.4% vs 56.6%) (P=0.002). Patients who had initial leukocyte counts of $< 20 \times 10^9/L$ had significantly better OS than children with initial leukocyte counts $\geq 20 \times 10^9/L$ (85.5% vs 64.8%) (P=0.012). Patients who did not have CNS involvement at diagnosis had significantly better EFS than those with CNS involvement at diagnosis (72.1% vs 35.3%) (P=0.000). Patients who did not have CNS involvement at diagnosis had significantly better OS than those with CNS involvement at diagnosis (79.6% vs 41.2%) (P=0.001). Children with a good response to prednisone on day 8 achieved significantly better EFS than those with a poor response to prednisone on day 8 (77.7% vs 29.5%) (P=0.000). Children with a good response to prednisone on day 8 achieved significantly better OS than those with a poor response to prednisone on day 8 (83.7%

Table 2. Analysis of Variables affecting EFS and OS

Characteristics	Categories	EFS (%)	P value	OS (%)	P value
Age	1-5 years	74.6	0.032*	82.2	0.043*
	≥ 6 yrs	62.7		69.8	
Gender	Male	68.6	0.623	76.4	0.731
	Female	75.2		81.3	
Type	B	72.6	0.011*	75.8	0.021*
	T	57.8		59.1	
Genetic alterations included in High Risk group#	Absent	79.9	0.001*	86.7	0.033*
	Present	53.5		66.2	
TLC	$< 20 \times 10^9/L$	78.4	0.002*	85.5	0.012*
	$\geq 20 \times 10^9/L$	56.6		64.8	
CNS	Not involved	72.1	0.000*	79.6	0.001*
	Involved	35.3		41.2	
Day 8 Prednisone response	Good	77.7	0.000*	83.7	0.012*
	Bad	29.5		36.4	
Risk	Standard	76.1	0.001*	85.9	0.032*
	Intermediate	70.3		78.6	
	High	50.2		57.4	

EFS-Event Free Survival, OS-Overall Survival; *-Significant p value; #Genetic alterations included in High Risk group of ALL-IC BFM2002 protocol are translocations t (9;22) and t (4;11)

vs 36.4%) ($P=0.012$). The EFS at 5 years was 76.1% for the SR group, 70.3% for the IR group, and 50.2% for the HR group ($P=0.001$). The OS at 5 years was 85.9% for the SR group, 78.6% for the IR group, and 57.4% for the HR group ($P=0.032$). There was no significant association between sex and survival rates ($P=0.731$).

Discussion

There are some limitations in this study. These include the retrospective nature which might have led to potential missing data, selection bias by only including patients who initiated treatment, and the impact of loss to follow-up.

The patients in the study received treatment in the Pediatric Oncology unit of a Cancer centre located in Northeast India. This institute serves as a tertiary referral centre and also offers training programs across multiple oncology specialities. Each year, our Pediatric Oncology clinic registers around 400 new cases of childhood malignancies. The clinic offers comprehensive services, including both inpatient and outpatient care, day care facilities, advanced diagnostic and therapeutic procedures, as well as 24/7 emergency and critical care support.

The outcome of childhood Acute Lymphoblastic Leukemia (ALL) in developing countries continues to be unfavourable. It is primarily due to various clinical and social challenges. Among the most significant of these is the limited availability of resources for both patients and healthcare providers [7]. Delays in diagnosis are common. They can affect both the tumour burden at presentation and the overall treatment outcome. However, it is challenging to measure the exact impact of such delays on clinical outcomes and presentation. Given its large population, India bears a significant share of the global burden of newly diagnosed cases of Acute Lymphoblastic Leukemia (ALL).

Advances in pediatric ALL treatment have been closely linked to deeper insights into leukemogenesis and a better understanding of the clinical, immunological, and biological diversity of the disease. The BFM group is widely acknowledged as one of the leading international scientific organizations dedicated to the treatment of pediatric Acute Lymphoblastic Leukemia (ALL). The ALL-BFM treatment protocols are among the most effective, enabling the attainment of excellent therapeutic outcomes. This led to the establishment of local scientific and clinical teams dedicated to treating pediatric ALL through BFM-oriented protocols. Consequently, successful multicentre studies were initiated in countries such as Germany, the Czech Republic, Poland, Greece, Austria, and across Latin America to evaluate the effectiveness of the ALL-IC BFM 2002 protocol. The ALL IC BFM 2002 protocol was implemented in an environment that differed from the highly structured settings of established cooperative groups. The key finding of this extensive intercontinental study was that 70% of patients achieved disease-free status, and 80% were still alive at the five-year follow-up. Treatment in developing countries often relies on protocols originally developed in Western nations. In India, data on the survival of

children with ALL is scarce and primarily confined to reports from individual centres. Research from India has demonstrated a gradual rise in overall survival (OS) rates over the past two decades. This is attributed to enhanced supportive care and the adoption of risk-adapted treatment approaches. The key factors contributing to poor survival included inadequate supportive care, high therapy-related mortality (TRM), treatment abandonment, and inconsistent adherence to treatment protocols.

In this present study, the mean age was 7.09 \pm 0.7 years and the median age was 6 years (Q1=4.3 years, Q3=8.5 years). Similar observations were seen in previous studies – median of 6 years by Bajel et al [8], mean of 5.6 \pm 0.23 years and median of 5 years by Kulkarni et al [9], median of 10 years by Radhakrishnan et al [10], mean of 6.04 years by Muriel et al [11], mean of 6.7 \pm 4.2 years and median of 6.8 years by Adalet et al [12]. 59.81% were males and 40.19% were females. An increased male-to-female ratio has also been reported in other studies [6, 8, 9, 10-12]. A study by Mohammad et al [13] showed that females predominated among ALL patients. 81.82% were B ALL, 18.18% were T ALL. More proportion of patients were found to be B ALL in other studies [6, 8, 10, 12, 14]. In contrast, T ALL was found more in a study by Mukhopadhyay et al [15]. The only genetic alterations included in the High Risk group of ALL-IC BFM 2002 protocol are the translocations t(9;22) and t(4;11), which together were present in 22 (5.26 %) patients.

In a study by Bajel et al [8], t(9;22) was found in 5.7% of patients. Arora et al [5] found the presence of translocation t(9;22) in 1.8% of patients. Stary et al [6] found the presence of genetic alterations of High Risk group in 3.8% of cases, of which 2.8% were t(9;22) and 1% were t(4;11). 48.80% patients had Total Leucocyte count (TLC) $<20 \times 10^9$ /L and 51.20% patients had TLC $\geq 20 \times 10^9$ /L count at presentation. The minimum TLC was 1.14×10^9 /L and the maximum TLC was 939.82×10^9 /L. The median TLC was 22×10^9 /L (Q1= 11.57×10^9 /L, Q3= 480.91×10^9 /L). The median was 10×10^9 /L in the study by Bajel et al [8]. Bajel et al found that 60.9% of patients had TLC $<20 \times 10^9$ /L and the 39.1% had TLC $\geq 20 \times 10^9$ /L. The mean TLC was 69.1×10^9 /L (range 0.6×10^9 /L - 849×10^9 /L) by Muriel et al [11]. Radhakrishnan et al [10] found that 39% of the patients had TLC below 20×10^9 /L and 61% had TLC $\geq 20 \times 10^9$ /L. CNS was involved in 3.83% of cases. In a study by Bajel et al [8], CNS involvement at diagnosis was present in 6.2% of the cases. Arora et al [5] found CNS disease in 2–6% of the patients, Radhakrishnan et al [10] in 3.4%, Stary et al [6] in 8%, Muriel et al [11] in 1.9%. Day 8 prednisone response was good in 83.97% of the cases and poor in 16.03% of cases. Similar responses were found in some other studies [7, 11]. Stary et al [6] found a good response in 90.2%, Moricke et al [16] found a good response in 92.5%. Another characteristic which could be analysed in this study was Vitamin D deficiency among ALL patients. A study by Nadirah et al [17] concluded that Vitamin D deficiency is highly prevalent in children with ALL, highlighting the need for regular Vitamin D screening and supplementation.

The following percentages are found in respective risk groups-Standard Risk (SR) group in 30.62%, Intermediate Risk (IR) group in 47.13%, and High risk (HR) group in 22.25% of the patients. Stary et al [6] found SR in 33%, IR in 48% and HR in 19% of patients. Valiev et al [18] found SR in 76.7%, IR in 18.5%, and HR in 4.8% of the patients. Kowalczyk et al [19] found SR in 32.6%, IR in 48.1% and HR in 19.3 % of patients. Konja et al [20] found SR in 35.5%, IR in 50.6%, and HR in 13.9% of the patients.

22.25% of the patients had a relapse. The majority of the relapses occurred within two years of diagnosis. The relapse rates were found to be different in other studies-15 % by Kowalczyk et al [19], 19% by Stary et al [6], 11.2% by Alecsa et al [21], 24.3% by Kulkarni et al [9], 2.3 % by Tzortzatou et al [14], 14.8% by Adalet et al [12]. Death occurred in 17.22 % of the patients in the study. In a study by Adalet et al [12], death occurred in 20.1% of the ALL patients. Katherine et al [22] reported the deaths in ALL patients in terms of mortality rates. The mortality rate was 1.7 for boys and 1.2 for girls 0-14 years of age.

The 5-year EFS and OS of all the patients were 69.5% and 72.3% respectively; 76.1% and 85.9% for the SR group, 70.3% and 78.6% for the IR group, and 50.2% and 57.4% for the HR group. Patients ≥ 6 years of age, T ALL, patients with the presence of genetic alterations of the High Risk group, higher initial leukocyte count, CNS involvement, and poor response to prednisone were found to have lower survival rates. The same protocol was used in some other studies with the following results. In the intercontinental study by Stary et al [6], at 5 years, the probabilities of EFS and OS were 74% and 82% for all patients; 81% and 90% for the SR, 75% and 83% for the IR, and 55% and 62% for the HR groups, respectively. Kowalczyk et al [19] found EFS and OS of 79% and 86% respectively; EFS of 90% for SR, 80% for IR, and 62% for HR at 5 years. Valiev et al [18] found 10-year EFS and OS of 84.1% and 91.8% respectively; 84 % and 92.8% for SR, 84.4% and 94.6% for IR and 63.5% and 71.1 % for HR. Konja et al [20] found 4-year EFS and OS of 88% and 89% respectively. Bahoush [23] found 5-yr EFS of 88.90%. In a study by Gao et al [24], the 5-year EFS was 71.7% in all patients, 75.6 % in the SR group, and 68.6 % in the IR group. Alecsa et al [21] found that the EFS of SR was 77.5% and HR was 37.7%. Katerina et al [25] found EFS and OS of 83.5% and 91.4% respectively ;89.4% and 98.1% for SR, 82.6% and 89.6% for IR and 68.8% and 78.1% for HR. Male sex and age above 10 years were adverse prognostic factors.

In a study by Bajel et al [8] using the BFM 76/79 protocol, the EFS and OS were 56% and 59.8% respectively. The 5-year OS and EFS were 46% and 43% respectively, by Kulkarni et al [9] using protocol UKALLX. Radhakrishnan et al [10] using protocol BFM-95 found that the EFS was 63.4%; risk stratification, sex, white blood cell count, day 8 blast clearance, and income were significantly associated with EFS. Advani et al [26], using the MCP 841 protocol, found EFS and OS were 49% and 53% respectively. In a study by Adalet et al [12] using the BFM 95 protocol, the EFS and OS were 78.4 % and 79.9 %, respectively. He found that children

in the standard-risk and medium-risk groups obtained statistically significant higher EFS and OS compared to the high-risk group. Children younger than 6 years old, patients who had initial leukocyte counts of $<20 \times 10^9/L$, B ALL, and children with a good response to prednisone on day 8 achieved significantly better EFS and OS. Children in the standard-risk and medium-risk groups obtained statistically significant higher EFS and OS compared to the high-risk group. Muriel et al [11] using ALL BFM 90, found 5-year EFS of 64%. There was significantly lower EFS in the high risk group. Paulo et al [27] found that among the cases of ALL, 70.7% were staged as CNS 1, with an observed survival probability of 75.0%.

Thus, we see that the survival in our study was less in comparison to the developed countries, but it was more than most of the previous studies in India. The reason for this in the present study may be related to patients presenting late to the institution, ignorance, and low nutritional status. Since it is evident from the present study that high risk group and intermediate risk groups are associated with lower EFS and OS than the standard risk group, we can adapt to a risk directed approach. In a study by Moricke et al [28], consistently favourable results in non-HR patients were achieved with significant treatment reduction in the majority of these patients. Another study by Moricke et al [29] showed that in parallel to relapse reduction, major efforts focused on reducing acute and late toxicity through advanced risk adaptation of treatment. Immunotherapy has significantly improved outcomes for children with acute lymphoblastic leukemia (ALL), particularly in relapsed or refractory (R/R) cases and for high-risk patients. Approved therapies like blinatumomab (a bispecific T-cell engager) and tisagenlecleucel (CAR T-cell therapy) have demonstrated high response rates and improved survival, with ongoing trials exploring their use in newly diagnosed patients to potentially reduce chemotherapy toxicity and further improve quality of life [30, 31].

In conclusion, survival outcomes in pediatric ALL were analysed, highlighting immunophenotype, cytogenetics, and established clinical factors as significant predictors of prognosis. The study demonstrates that, with proper risk stratification and corresponding treatment modifications, it is feasible to administer an effective regimen in India and achieve satisfactory event-free and overall survival outcomes. Managing children with ALL in India presents multiple challenges for pediatric oncologists, including high rates of treatment abandonment, loss to follow-up, mortality, and malnutrition. It is essential to implement measures aimed at educating both families and healthcare staff to reduce therapy abandonment and to mobilize resources that better support families coping with the challenges of childhood cancer. Enhancements in supportive care, coupled with financial assistance from government and non-governmental agencies, could significantly reduce therapy abandonment rates and, consequently, lower mortality.

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Ethics approval

Institutional Ethics Committee approval was obtained prior to the study.

Conflicts of Interest

The authors declare no conflict of interest.

Patients' consent form

Applied for waiver of consent form due to the study's retrospective nature.

Scientific Committee approval reference number

BBCI-TMC/SC/Appr/225/2022.

Institutional Ethics Committee (IEC) approval reference number

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