Original Article

# Outcomes of acute lymphoblastic leukemia in children and young adults treated with a Berlin-Frankfurt-Münste-based protocol in a tertiary care multispecialty government hospital

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## Abstract

**Background:** While the survival of childhood acute lymphoblastic leukemia (ALL) approaches 90% in developed nations, outcomes in developing countries are much lower.

**Methods:** We conducted a retrospective analysis of the first 50 patients aged <25 years with newly diagnosed ALL who were treated with a modified Berlin–Frankfurt–Münster (BFM)-2009 protocol at our tertiary care government hospital between May 2020 and December 2024. All patients were followed up until December 2025.

**Results:** The median age was 6 years with a male-to-female ratio of 1.5:1. Thirty-six patients had pre-B-cell ALL and 14 had T-cell ALL. On day 8, seven patients (14%) had poor prednisone response and 43 (86%) had good prednisone response. The complete remission rate at the end of induction was 94%. Forty-three patients (86%) achieved measurable residual disease negative status. According to BFM-2009 stratification, 12 were standard risk (SR), 30 were intermediate risk (IR), and 8 were high risk (HR). One patient abandoned treatment, seven patients relapsed, and three died of treatment-related toxicity. At 3 years, the event-free survival (EFS) and overall survival for the entire cohort were 75.2% and 78.3%, respectively. The SR, IR, and HR groups achieved an EFS of 90.0%, 73.3%, and 62.5%, respectively, at 3 years.

**Conclusion:** The use of a modified risk-adapted Western protocol was feasible in a government hospital setting without undue toxicity or mortality.

**Keywords:**
Acute lymphoblastic leukemia, BFM protocol, developing country, survival outcomes

## Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. By using current treatment protocols, the survival of childhood ALL is 80–90% in most developed countries.[1,2] In India, studies from 1985 – 2011 reported event-free survival (EFS) from 41 to 70% and overall survival (OS) from 45 to 81%.[3-8] In the last 15 years, Indian centers have used risk-stratified protocols with improvement in EFS (70–82%) and OS (78–88%).[9-15]

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The lower survival rates from developing countries like India can be attributed to late presentation, referral delays, poor socioeconomic status, malnutrition, inadequate supportive care, and high infectious mortality.[6,10]

Our hospital is a tertiary care multispecialty government hospital. The treatment is free to all residents of the state and is highly subsidized for all others. The Department of Medical Oncology was established in late 2018. Till then, all children with ALL were referred outside the state for treatment. In 2020, after ensuring that basic infrastructure was in place and that adequate nurses had been trained, the department started treating children with ALL.

This is a retrospective review of the first 50 patients with ALL, under 25 years of age, treated with a modified Berlin-Frankfurt-Münster (BFM)-2009 protocol.[16,17]

## Methods

Between May 1st, 2020, and December 31st, 2024, 50 patients under 25 years of age, with newly diagnosed ALL, were started on treatment with a modified BFM 2009 protocol. We reviewed their medical records and follow-up till December 31st, 2025.

The diagnosis was established by a bone marrow aspiration revealing more than 25% lymphoblasts. Immunophenotyping by flow cytometry, karyotyping, and real-time polymerase chain reaction for recurrent translocations was performed on bone marrow aspirate/peripheral blood.

At diagnosis, all patients had a complete hemogram, biochemistry profile including renal and liver function tests, coagulation profile, serology for human immunodeficiency virus, hepatitis B and hepatitis C, and blood group typing. Cardiac evaluation with electrocardiogram (ECG) and two-dimensional echocardiography was done for all patients, as was imaging with chest X-ray. Additional imaging with ultrasonography and computed tomography was performed if clinically indicated.

All the patients underwent diagnostic lumbar puncture at the beginning of therapy. Central nervous system involvement was stratified as central nervous system (CNS) 1, 2, and 3 as per standard criteria.

### Risk stratification

Risk stratification according to BFM 2009 included age at presentation, initial white blood cell count, cytogenetic features, day 8 prednisone response, and day 33 (Time point 1 – TP1) measurable residual disease (MRD) by flow cytometry [Figure 1]. Absolute blast count (ABC) less than 1000/cmm on day 8 of initiating prednisone was defined as prednisone good response (PGR) and ABC more than 1000/cmm was defined as poor prednisone response (PPR). Bone marrow assessments on day 15 were not performed. The end of induction bone marrow was defined as M1, M2, or M3 as per standard criteria. Negative MRD status was taken as <0.01% blasts on flow cytometry. Patients were assigned to standard risk (SR), intermediate risk (IR), or high risk (HR) categories as per BFM risk stratification and received risk-adapted therapy.

### Treatment

All patients were treated with a modified BFM-2009 protocol. Complete blood count was monitored prior to each chemotherapy dose. Kidney and liver functions were monitored before starting a new block or as and when clinically indicated. Patients received prophylactic intrathecal methotrexate or triple intrathecal therapy with methotrexate, cytarabine, and hydrocortisone as per protocol.

Modifications to the original protocol practiced at our institute were as follows:

1. Two doses of Pegylated asparaginase 1000 IU/$m^2$ 14 days apart were used instead of L-asparaginase in Induction 1A and one dose of Pegylated asparaginase 1000 IU/$m^2$ was used in Reinduction A.
2. We used 6-mercaptopurine (6-MP) instead of 6-thioguanine (6-TG) in view of non-availability.
3. Vindesine was replaced by vincristine 1.5 mg/$m^2$ during high-risk blocks.
4. Daunorubicin was given a 2 hours infusion instead of 24 hours in high-risk blocks 2 and 5.

Standard and intermediate-risk patients received Induction A and B, protocol M, and reinduction A and B, followed by 18 months of maintenance chemotherapy. The dose of methotrexate during protocol M was 2 g/$m^2$ in SR patients and 5 g/$m^2$ in IR patients. Patients with high risk received 6 high-risk blocks after Induction 1B, followed by bone marrow assessment for MRD, then reinduction A and B and maintenance therapy for 18 months. During the intensive phase of treatment, SR and IR patients received 11 doses of intrathecal therapy and HR patients received 13 doses.

### Statistical analysis

EFS was defined as the time from diagnosis to the first occurrence of an adverse event, which included relapse, abandonment of treatment, or death. OS was calculated from the date of diagnosis to the date of death from any cause or the last follow-up. Survival probabilities were estimated using the Kaplan-Meier method. All statistical analyses were performed using R software.

## Key Message

*Implementing a modified BFM-2009 protocol in a tertiary level government hospital is feasible. It is an effective strategy for children and young adults with acute lymphoblastic leukaemia without undue treatment related mortality.*

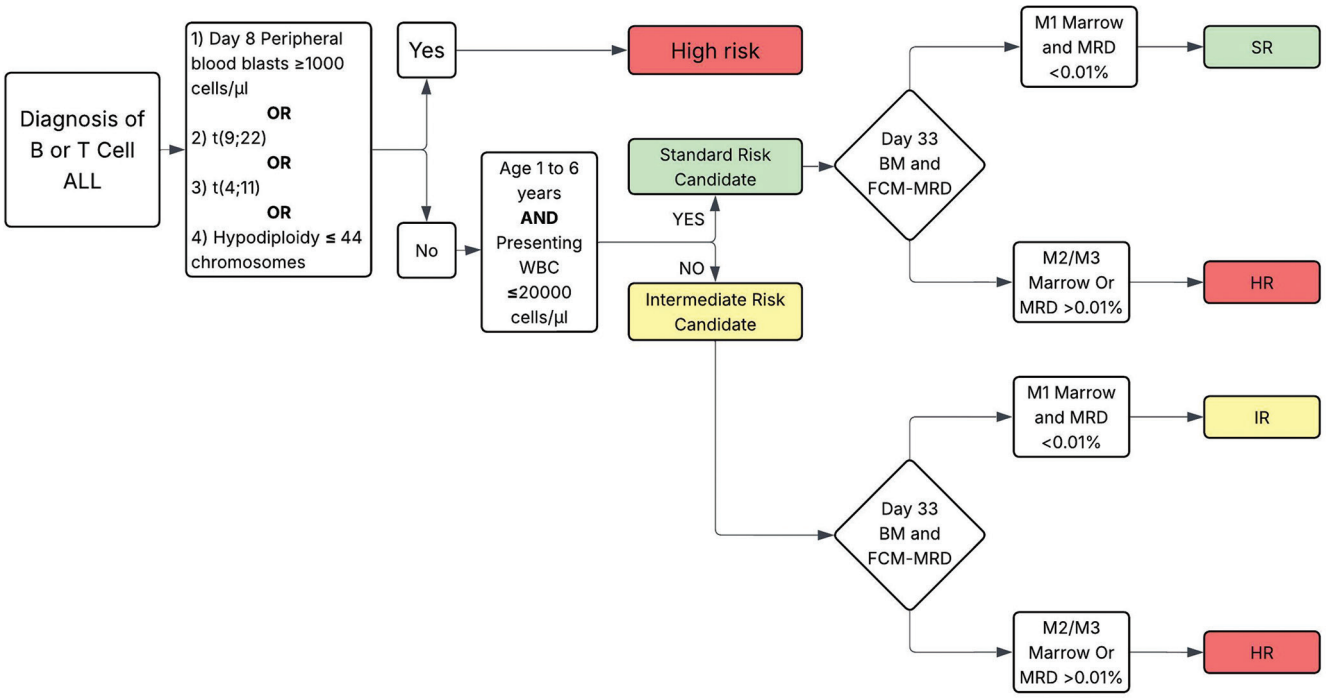


**Figure 1: Risk stratification as per BFM-2009. BFM = Berlin–Frankfurt–Münster**

## Results

During May 2020 to December 2024, the department registered 5,562 new cancer patients. Of these, 276 (5%) were under 25 years of age. Of these 276 patients, 50 patients had newly diagnosed ALL and were reviewed in this study.

### Patient characteristics

There were 30 boys (60%) and 20 girls (40%) in our cohort. The median age at diagnosis was 6 years (range 1–25 years). Forty were residents of Goa, 7 were from Maharashtra, 2 were from Karnataka, and 1 was from Uttar Pradesh.

### Presenting features

The median duration of symptoms was 12 days. Fever was the most common symptom, observed in 45 patients (90%), followed by abdominal pain in 15 (30%), arthralgia in 11 (22%), and cough in 8 (16%). Hepatosplenomegaly was present in 32 patients (64%), while mediastinal masses were noted in 3 patients (6%) and lymphadenopathy in 23 patients (46%). None of the patients had testicular or CNS involvement at presentation. At presentation, 32 patients had hemoglobin <8 g/dL (64%), 7 patients had WBC >100,000/µL (14%), and 27 patients had platelets <50,000/µL (54%). Tumor lysis syndrome occurred in 5 patients (10%). All the patients were treated with hyperhydration; two received rasburicase. None of the patients required dialysis.

### Disease characteristics and treatment

A total of 36 patients (72%) had B-ALL, while 14 (28%) had T-ALL. Karyotyping revealed diploidy in 34 patients (68%), hyperdiploidy in 8 patients (16%), and was not done or was inconclusive in 8 patients (16%). Presence of t (12;21) was seen in 2 patients (4%), t (1;19) in 1 patient (2%), E2A-PBX1 in 1 patient (2%), and T-cell receptor gene rearrangement in 1 patient (2%).

### Induction response and risk stratification

Hemogram on the 8$^{th}$ day of induction revealed PGR in 43 patients (86%) and PPR in 7 patients (14%). There was one induction death due to neutropenic sepsis. Forty-seven patients had M1 marrow, one had M2 marrow, and one had M3 marrow at the

end of induction. The complete remission (CR) rate was 94%. Forty-three patients (86%) achieved MRD-negative status, while 6 patients (12%) remained MRD-positive at the end of induction.

Risk stratification at the end of induction revealed standard risk in 12 patients (24%), intermediate risk in 30 patients (60%), and high risk in 8 patients (16%). One patient abandoned treatment after completing induction.

Nine patients (18%) received HR blocks (8 HR patients and 1 IR patient with hyperleukocytosis at presentation). Thirty-nine patients (78%) received high-dose methotrexate-based consolidation. Those receiving HR intensification had longer overall treatment duration (median 309 days, range 261–390) compared to those on standard intensification (median 245 days, range 181–322).

### Survival outcomes

Two patients died in remission, one due to tuberculous meningitis, and one due to neutropenic septic shock. Seven patients (14%) relapsed. Two patients had a very early relapse, and five patients had an early relapse. All the relapses involved bone marrow, with one patient developing a concurrent CNS relapse. Of these, six patients died, and one is alive in second remission. Thirty-nine (78%) patients are alive in first remission. Of these, 29 patients have completed treatment, and 10 patients are still on maintenance therapy.

At 3 years, the EFS and OS for the entire cohort were 75.2% (95% confidence interval [CI], 63.3%–89.4%) and 78.3% (95% CI, 67.2%–91.2%), respectively [Figure 2]. The EFS for SR, IR, and HR were 90.0% (95% CI, 73.2%–100%), 73.3% (95% CI, 57.8%–93%), and 62.5% (95% CI, 36.5%-100%) and OS were 90.0% (95% CI, 73.2%–100%), 78.6% (95% CI, 64.7%–95.5%), and 62.5% (95% CI, 36.5%–100%), which were statistically insignificant (EFS *P* value 0.5, OS *P* value 0.51) due to lack of statistical power caused by small subset sample size in SR and HR groups [Figure 2].

## Discussion

Our hospital is the only tertiary care government facility in the state. The Department of Medical Oncology was set up in August 2018. As patient referrals were building up, the first 12–18 months were utilized to train resident doctors and nurses and to put protocols and processes in place. During this time, children with ALL were referred outside the state for treatment, as was the practice before the department came into being. In March 2020, the COVID-19 pandemic started, and patients were unable to travel outside the state. In May 2020, the department started treating children with ALL.

Being a tertiary-level multispecialty teaching hospital, laboratory services for basic hematology, biochemistry, and microbiology are available in-house. Advanced diagnostic tests like flow cytometry, karyotyping, real-time polymerase chain reaction (RT-PCR), and fluorescent-in-situ-hybridization were outsourced to private laboratories outside the state. Methotrexate drug-level monitoring was standardized and performed in-house. Blood components were available in our blood bank, and apheresis for single-donor platelets became available in 2021 during the COVID pandemic.

The treatment of childhood ALL is complex, intense, and prolonged. The first challenge is having the

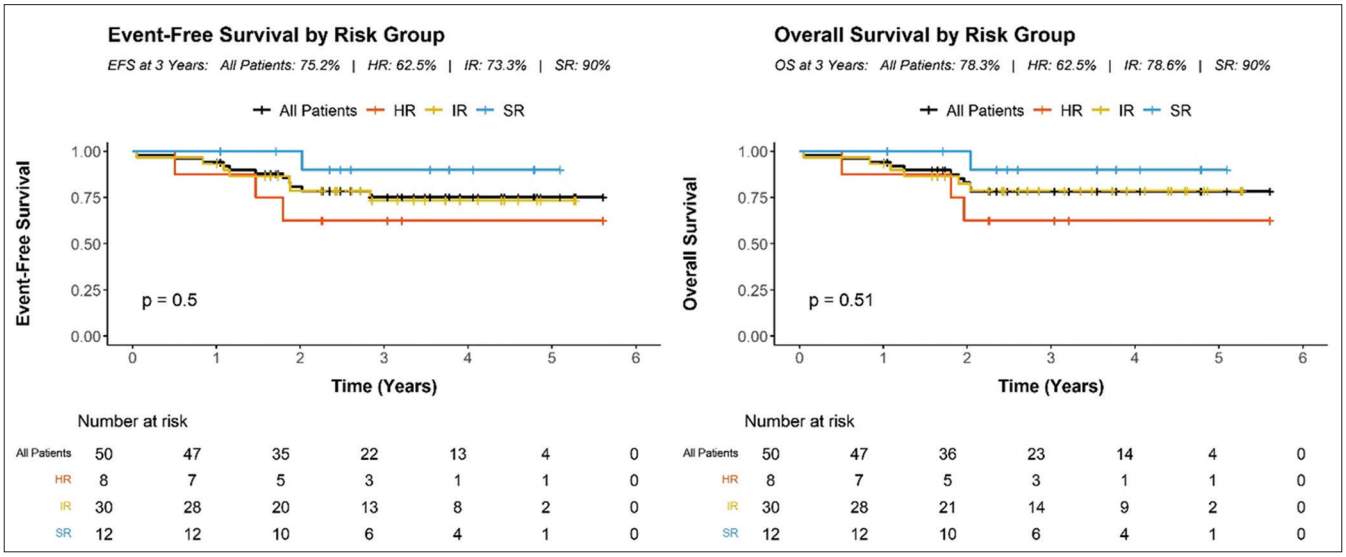


**Figure 2: EFS and OS for all patients, SR, IR, and HR groups. EFS = Event-free survival, OS = Overall survival, SR = Standard risk, IR = Intermediate risk, HR = High risk**

right health-seeking behavior in the population. The presenting symptoms of childhood ALL can sometimes be vague, leading to a delay in seeking appropriate treatment. The next challenge is delayed referral by primary care health professionals to specialists. Unless primary care doctors are sensitized to the varied presentations of childhood cancer in general and ALL in particular, referral delays will remain a hurdle to timely diagnosis. In our patient population, the mean duration of symptoms before diagnosis was 12 days, with a range of 2 to 60 days. This compares favorably with other studies from India reporting more than 40 days.[7,18] The study from North India has correlated higher mortality in patients with a longer symptom diagnosis interval.[7,18] The higher health awareness and cohesive health system in our state could explain this short symptom diagnosis interval.

The age and sex distribution, presenting features, and immunophenotypic pattern in our population were similar to those reported from other series in India. The induction mortality of 2% and remission rate of 94% were also similar to other studies from India. Our MRD-positive rate at the end of induction was 12%, which is lower than other series. This could be due to the false-negative MRD status, as our samples were processed outside the state and could have degenerated in transit. This could have resulted in truly high-risk patients being under-stratified into SR or IR groups. This logistical constraint will be rectified by starting in-house flow cytometry facility in our upcoming cancer center.

We could successfully administer high-dose methotrexate to all patients without undue toxicity. The two remission deaths were related to infections. There was no morbidity or mortality related to bleeding. All our relapses were very early or early and could not be salvaged with chemotherapy alone.

Our low rates of abandonment and infectious mortality can be attributed to many factors. All patients from Goa and Maharashtra received free treatment through government schemes, and the remaining three patients were supported by non-government organizations (NGOs). We have developed a structured support system wherein counselors and social workers provide continuous education regarding early recognition of danger signs, reinforce treatment adherence, and emphasize the importance of presenting to the hospital at the earliest onset of symptoms. This proactive counseling ensures that parents are sensitized to seek medical

**Table 1: Comparison with other Indian studies**

| | Radhakrishnan *et al.*[9] | Khandelwal *et al.*[11] | Kumar *et al.*[12] | Thakkar *et al.*[13] | Sriram *et al.*[14] | Khera *et al.*[15] | Present Study |
|---|---|---|---|---|---|---|---|
| Institute | Adyar, Chennai | BLK-Max hospital, Delhi | AIIMS Rishikesh | Medanta, Gurugram | Indraprastha Apollo, Delhi | Army hospital, Delhi | GMC, Goa |
| Period | 2005-2011 | 2011-2021 | 2021-2023 | 2016-2021 | 2002-2024 | 2018-2024 | 2020-2024 |
| Age Range | <30 years | 1-18 years | 1-24 years | 1–17 years | 1-18 years | <14 years | 1–25 years |
| N | 238 | 100 | 75 | 68 | 410 | 166 | 50 |
| Protocol Backbone | BFM 95 | BFM 2002 | BFM 2009 | BFM-95 | Modified COG | BFM 2009 | BFM 2009 |
| EFS-all | 63.4% (at median f/u of 32.7 months) | 80% (at median f/u of 60 months) | 65.3% | 79.4% (at median f/u) | 81.9% at 5 years | 82.5% (at median f/u of 36.5 months) | 75.2% at 3 years |
| EFS-HR | NR | 55% | NR | NR | NA | 76.9% | 62.5% |
| EFS-IR | NR | 85% | NR | NR | NA | 83% | 73.3% |
| EFS-SR | NR | 89% | NR | NR | 88.5% | 95.7% | 90% |
| OS-all | NR | 82% (at median f/u of 60 months) | 74.2% | 88.2% (at median f/u) | 84.1% at 5 years | 86.1% (at median f/u of 36.5 months) | 78.3% at 3 years |
| OS-HR | NR | 60% | 64% | NR | NA | 79% | 62.5% |
| OS-IR | NR | 87% | 84% | NR | NA | 85% | 78.6% |
| OS-SR | NR | 89% | 80% | NR | 91.6% | 96.5% | 90% |
| Relapse | 31% | 7% | 6.4% | 14.7% | 10% | 9.6% | 14% |
| Induction Mortality | 3.3% | 6% | 12% | 1.36% | 1.7% | 1.2% | 1.8% |
| Treatment-related mortality | NR | 5% | NR | 4.4% | 1.9% in SR and 3.9% in HR group | 4.9% | 6% |
| Abandonment | 5.5% | NR | 12% | 18% | NR | NR | 1.8% |

BFM=Berlin–Frankfurt–Münster, EFS=Event-free survival, OS=Overall survival, HR=High risk, IR=Intermediate risk, SR=Standard risk, NR=Not reported, NA=Not applicable

attention promptly, thereby allowing timely intervention and reducing mortality. For patients staying far, temporary accommodation is provided near the hospital during intensive phase cycles at a nominal cost. Ration support is provided for poor families through NGOs.

For a start-up department, we managed to achieve an EFS of 75.2% and an OS of 78.3% at a median follow-up of 40.2 months (range 1–68 months). Due to the small subset size in the SR and HR groups, we could not document a statistically significant difference in survival between various risk groups, as is expected in patients with childhood ALL. Table 1 compares our study with other studies from India. We are aware that these numbers are likely to drop due to late relapses.

The state of Goa ranks high on multiple health indices. The literacy rate in Goa (88.7%) is much higher than the national average of 73%. The infant mortality rate (5 deaths per 1000 live births in 2020) and total fertility rate (1.3 children per woman in 2019-21) are much lower than the national benchmarks.[19] Goa has one of the highest life expectancies in India, of 72–74 years.[20] However, there is a paucity of data on cancer incidence and cancer survival from Goa.[21] We hope this study will prove a valuable addition to the existing data and help shape cancer care policy in the state.

## Conclusion

This 5 years of experience has taught us that it is feasible to treat children and young adults with ALL with a modified Western protocol in our setup. Upgrading our laboratory support services will ease the diagnostic process and reduce errors that can occur with transporting samples over long distances. Having access to in-house stem cell transplant services may help to salvage some early relapses and improve OS.

### Ethics committee approval and consent

This retrospective study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Ethics Committee. Given the retrospective nature of the study utilizing anonymized medical records, the requirement for informed patient consent was waived by the Ethics Committee.

### Data availability statement

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

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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## References

1. Pui CH, Yang JJ, Hunger SP, Pieters R, Schrappe M, Biondi A, *et al*. Childhood acute lymphoblastic leukemia: Progress through collaboration. J Clin Oncol 2015;33:2938-48.
2. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, *et al*. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: A report from the children's oncology group. J Clin Oncol 2012;30:1663-9.
3. Advani S, Pai S, Venzon D, Adde M, Kurkure PK, Nair CN, *et al*. Acute lymphoblastic leukemia in India: An analysis of prognostic factors using a single treatment regimen. Ann Oncol 1999;10:167-76.
4. Magrath I, Shanta V, Advani S, Adde M, Arya LS, Banavali S, *et al*. Treatment of acute lymphoblastic leukaemia in countries with limited resources; lessons from use of a single protocol in India over a twenty year peroid. Eur J Cancer 2005;41:1570-83.
5. Mukhopadhyay D, Gupta P, Mukhopadhyay S, Chitalkar P, Banavali SD, Advani SH, *et al*. Result of childhood acute lymphoblastic leukemia protocol (INCTR) from a developing country. J Clin Oncol 2007;25(18_Suppl):20015.
6. Bajel A, George B, Mathews V, Viswabandya A, Kavitha ML, Srivastava A, *et al*. Treatment of children with acute lymphoblastic leukemia in India using a BFM protocol. Pediatr Blood Cancer 2008;51:621-5.
7. Kulkarni KP, Marwaha RK, Trehan A, Bansal D. Survival outcome in childhood ALL: Experience from a tertiary care centre in North India. Pediatr Blood Cancer 2009;53:168-73.
8. Arya LS, Padmanjali KS, Sazawal S, Saxena R, Bhargava M, Kulkarni KP, *et al*. Childhood T-lineage acute lymphoblastic leukemia: Management and outcome at a tertiary care center in North India. Indian Pediatr 2011;48:785-90.
9. Radhakrishnan V, Gupta S, Ganesan P, Rajendranath R, Ganesan TS, Rajalekshmy KR, *et al*. Acute lymphoblastic leukemia: A single center experience with Berlin, Frankfurt, and Munster-95 protocol. Indian J Med Paediatr Oncol 2015;36:261-4.
10. Nath UK, Chattopadhyay D, Bakliwal A, Vaniyath S, Chetia R, Rajoreya AK. Encouraging results with ALL IC-BFM 2009 protocol therapy in pediatric acute lymphoblastic leukemia/lymphoma in resource-limited setting: A single-center study from India. Blood 2019;134:5118.
11. Khandelwal V, Choudhary D, Sharma SK, Doval D, Handoo A, Dadu T, *et al*. Treatment of newly diagnosed paediatric acute lymphoblastic leukaemia on BFM-based chemotherapy protocol: Feasibility and outcome from a tertiary care center in India. Pediatr Hematol Oncol J 2023;8:218-23.
12. Kumar K, Singh SK, Nayak J, Rajamani K, Gupta A, Satadeve P, *et al*. Outcome of childhood and adolescents and young adults ALL treated with ALL IC-BFM 2009 protocol-A single-center experience in India. Indian J Hematol Blood Transfus 2025;41:494-503.
13. Thakkar D, Upasana K, Udayakumar DS, Rastogi N, Chadha R, Arora S, *et al*. Treatment of pediatric acute lymphoblastic leukemia in India as per modified BFM 95 protocol with minimal residual disease monitoring. Hematology 2025;30:2439733.
14. Sriram M, Bhosle S, Mahajan A. Outcomes with risk-stratified treatment algorithm for childhood ALL in India. J Pediatr Hematol Oncol 2026;48:40-3.
15. Khera S, Muhammed MKS, Kumar R, Kapoor R. Outcomes of childhood acute lymphoblastic leukemia treated with modified BFM-2009 protocol using measurable residual disease-based risk-stratification: A single-center study. Indian Pediatr 2026. doi: 10.1007/s13312-026-00277-9.
16. Campbell M, Castillo L, Janic D, Belgrad S, Konja J, Kovacs G, *et al*. A randomized trial of the I-BFM-SG for the management of childhood

non-B acute lymphoblastic leukemia. Bialaczka.org. 2009. Available from: https://www.bialaczka.org/wp-content/uploads/2016/10/ALLIC_BFM_2009.pdf. [Last accessed on 2026 Mar 31].
17. Campbell M, Kiss C, Zimmermann M, Riccheri C, Kowalczyk J, Felice MS, *et al*. Childhood Acute Lymphoblastic Leukemia: Results of the Randomized Acute Lymphoblastic Leukemia Intercontinental-Berlin-Frankfurt-Münster 2009 Trial. J Clin Oncol 2023;41:3499-511.
18. Sampagar A, Patil NG, Reddy NA, Dias M. ALL induction outcome: Real-world data from a pediatric oncology center in an LMIC setup with rural predominance. Indian J Cancer 2024;61:215-23.
19. NITI Aayog. Summary Report: Goa. New Delhi: National Institution for Transforming India, Government of India; 2025. Available from: https://www.niti.gov.in/sites/default/files/2025-07/Summary-Report-Goa%20%281%29.pdf. [Last accessed on 2026 Mar 22].
20. National Health Systems Resource Centre. State Health Dossier 2021: Goa. New Delhi: Ministry of Health and Family Welfare, Government of India; 2021. Available from: https://nhsrcindia.org/sites/default/files/practice_image/HealthDossier2021/Goa.pdf. [Last accessed on 2026 Mar 22].
21. Nayak CA, Chodankar SN, Afonso B, Loliyekar AV, Pereira MI. Incidence and trends of cancer in Goa, India: A single center retrospective study. Int J Community Med Public Health 2025;12:4646-51.