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Impact of End-of-Induction Minimal Residual Disease on Survival in Pediatric B-ALL: A Retrospective Study from a New Pediatric Oncology Center in Central India

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Abstract
Minimal residual disease (MRD) is a strong prognostic indicator in pediatric B-precursor acute lymphoblastic leukemia (B-ALL). This study examines the relationship between end-of-induction MRD and various factors, including overall survival at a tertiary care center in central India. We retrospectively analyzed 65 patients with Acute lymphoblastic leukemia (ALL) who received induction therapy according to the ICICLE 2014 protocol between 2018 and 2023, followed up till July 2024. MRD status was assessed at the end of induction therapy, with a cutoff level of <0.01% considered MRDnegative. Factors, including age, total leukocyte count (TLC), response to prednisolone, cytogenetics were analyzed. We used Kaplan-Meier survival analysis to evaluate the impact of MRD status on overall survival. The 65 patients included 41 who were MRD-negative and 24 who were MRD-positive after induction therapy. Patients with MRD-positive status had significantly poorer overall survival. Positive MRD was noted in relapsed patients, 66.67% of patients who relapsed and died had positive MRD. MRD-positive patients tended to be older, have a less favorable response to prednisolone and present with higher initial TLC, though these trends were not statistically significant. The 2-year overall survival rate was 80.5% for MRD-negative patients, compared to 62.5% for MRD-positive patients. These findings demonstrate the importance of achieving MRD-negative status and support using MRD assessment for risk stratification in ALL treatment.

INTRODUCTION

Minimal residual disease (MRD) refers to the presence of small numbers of cancer cells that persist despite complete remission on conventional pathology. MRD detection is a crucial prognostic tool across hematological malignancies, strongly associated with relapse risk, particularly in acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL) and multiple myeloma[1-4]. In chronic myeloid leukemia (CML), monitoring BCR-ABL mRNA levels in peripheral blood is a key method for assessing treatment response and disease progression[2,3]. In ALL, MRD positivity has been linked to worse event-free survival (EFS) and overall survival (OS), influencing treatment intensification or deescalation strategies[5,6]. In India, childhood ALL survival rates (~65%) remain lower than global standards due to factors such as delayed diagnosis, poor initial health status, inadequate risk stratification, and chemotherapy-related complications. Treatment interruptions and patient migration further impact outcomes. The Indian Collaborative Childhood Leukemia (ICiCLe) study group was initiated in 2012 to address these challenges and improve pediatric leukemia management[7]. MRD is an independent predictor of survival in both pediatric and adult ALL, guiding risk stratification and therapy modification[8-9]. However, its prognostic value must be considered alongside age, WBC count, cytogenetics and therapy response[4]. MRD assessment employs multiparametric flow cytometry (MFC), PCR-based detection of IgH/TCR rearrangements, and fusion transcript analysis (e.g., BCR-ABL), though inter-study variability and sensitivity differences necessitate standardization[10,11]. Minimal residual disease (MRD) is a key indicator of residual disease burden after therapy, reflecting therapeutic effectiveness. MRD status influences clinical management, trial design and drug development, but its broader implementation as an endpoint has been limited due to challenges in data interpretation across different studies, treatments and patient profiles. Our retrospective study examines the relationship between end-of-induction MRD and survival outcomes in pediatric ALL at a tertiary care center in Central India, aiming to strengthen risk-adapted treatment approaches and improve outcomes.

MATERIALS AND METHODS

Study Design and Patient Selection: This retrospective study was conducted in the Pediatric Hemato-Oncology Unit at a tertiary care institute in Central India. Medical records of 65 pediatric ALL patients (aged 1-18 years) treated with ICiCle-2014 protocol (2018-2023) and followed until July 2024 were analyzed. Patients <1 year and those with Down syndrome were excluded due to different treatment protocols. The study was approved by the institutional review board and informed consent was obtained per the Declaration of Helsinki.

Diagnosis and Risk Stratification: ALL diagnosis was confirmed through bone marrow and/or peripheral blood morphology, supplemented by flow cytometry (FCM). Cytogenetic analysis (FISH, ploidy analysis) aided in risk stratification, classifying patients as standard-risk (SR), intermediate-risk (IR), or high-risk (HR). CNS involvement was assessed via cerebrospinal fluid (CSF) cytomorphology. (Table 1)

Table 1: Risk Stratification as Per IciCle

Characteristics	Standard risk	Intermediate risk	High risk
Age at diagnosis	>1 years and <10 years	>10 years	
Bulk of disease		bulky lymph nodes (=5 cm in peripheral region and in chest >5 cm on CT scan or occupying =1/3rd diameter on chest x-ray) and/or bulky liver/spleen reaching beyond midway to umbilicus and/or presence of testicular disease	
Leucocyte at diagnosis	<50,000/cumm	>=50,000/cumm	
Response to steroid at day 8			Poor response (Presence of=1000 blasts/ml)
End of induction MRD			>0.01%
Cytogenetics	High hyperdiploidy (modal chromosome number 51-67) ETV6/ RUNX1 fusion translocation [t(12;21) (p13; q22)		BCR-ABL/MLL re arrangements Hypodiploidy (> 45 chromosomes)
Immunophenotype			T ALL
CNS Disease	Absent	Absent	Present

Response Assessment and MRD Evaluation: At the end of induction (Day 35), response assessment included bone marrow morphology (M criteria for ALL) patients achieving M0 to M1 status (with blast cells <5%) were deemed responders and considered in chromosome-positive patients underwent qPCR-based BCR-ABL transcript assessment. For high-risk cases (MRD-positive post-induction, MLL translocations, or poor prednisolone response), repeat MRD testing was conducted after consolidation.

Treatment and Follow-up: Patients received chemotherapy largely on an outpatient basis, except for those requiring high-dose methotrexate or hospitalization for Grade 3/4 toxicities. Patients with MRD-positive at the end of induction underwent treatment escalation.

Statistical Analysis: Data were analyzed using SPSS v25.0. Descriptive statistics (mean, SD, frequency) were computed at a 95% confidence interval. Kaplan-Meier survival analysis, Log-rank test and Cox proportional hazards model were used to evaluate MRD's impact on overall survival (OS). Additional factors analyzed included age, total leukocyte count (TLC), prednisolone response and cytogenetics.

RESULTS AND DISCUSSIONS

Clinicodemographic Characteristics (Table 2): The study included 65 patients with a mean age of 6.09

years (SD: 3.51). Age distribution was 53.85% (0-5 years), 33.85% (6-10 years), and 12.31% (11-16 years). The gender ratio was nearly equal (50.7% male, 49.3% female). At the last follow-up, 38.46% were alive and disease-free, 26.2% were on treatment, 15.4% had died, 6.2% were living with relapse and 4.6% had undergone BMT post-relapse. The mean total leukocyte count (TLC) at diagnosis was 43,216.15 (SD: 69,795.76), with 41.54% presenting with TLC <10,000 and 13.85% with TLC >100,000. MRD negativity at the end of induction was noted in 63.8%, while 36.2% were MRD-positive. Good prednisolone response was seen in 92.3%, with 7.7% classified as poor responders. On average, chemotherapy was withheld for 2.62 days (SD: 5.75), but 66.2% had no delays. Cytogenetic analysis revealed 70.8% had normal results, with ETV6/RUNX1 (7.7%), BCR/ABL, MLL and TCF3/PBX1 abnormalities in smaller proportions. Karyotyping showed 92.3% normal, 6.2% hyperdiploid and 1.5% hypodiploid cases. The mean overall survival (OS) was 650.86 days (SD: 463.99). Survival rates were 38.5% (<1 year), 29.2% (1-2 years), 21.5% (2-3 years) and 10.8% (>3 years).

Table 2: Clinicodemographic Characteristics

Parameters	No. of patients (%)
Age	
Mean+SD in years	6.09 + 3.51
0-5 years	35 (53.85%)
6-10 years	22 (33.85%)
11-16 years	8 (12.31%)
Gender	
Male	33 (50.7%)
Female	32 (49.3%)
Patient Status	
Relapse, living with disease	4 (6.2%)
Relapse, BMT	3 (4.6%)
Dead	10 (15.4%)
Alive on treatment	17 (26.2%)
Alive on follow-up/disease-free	25 (38.46%)
Relapse, dead	6 (9.23%)
TLC at presentation	
Mean + SD	43,216.15+ 69,795.76
<10,000	27 (41.54%)
10,000-50,000:	24 (36.92%)
50,000-100,000	5 (7.69%)
>100,000:	9 (13.85%)
MRD at end of induction	
Negative	41 (63.8%)
Positive	24 (36.2%)
Prednisolone response	
Good prednisolone response	60 (92.3%)
Poor prednisolone response	5 (7.7%)
Number of days chemo withheld	
Mean + SD	2.62 + 5.75
0 days	43 (66.2%)
1-7 days	14 (21.5%)
8-30 days	8 (12.3%)
Cytogenetics/FISH	
Negative	46 (70.8%)
ETV6/RUNX1	5 (7.7%)
BCR/ABL	1 (1.5%)
MLL	1 (1.5%)
TCF3/PBX1	4 (6.2%)
Not reported	8 (12.3%)
Karyotyping	
NA/Normal	60 (92.3%)
Hyperdiploid	4 (6.2%)
Hypodiploid	1 (1.5%)
Overall Survival Period (days)	
Mean + SD	650.86 + 463.99
< 1 years	25 (38.5%)
1-2 years	19 (29.2%)
2-3 years	14 (21.5%)
3 years	7 (10.8%)

MRD Status and Clinical Parameters (Table 3): Multivariate analysis between MRD Positive (36.2%) and Negative (63.8%) groups showed no statistically significant differences due to small sample size.

Age: MRD-Positive patients had a slightly higher mean age (6.40 vs. 5.91 years, p=0.58).

Gender: MRD-Positive patients had 54.17% males vs. 48.78% in MRD-Negative (p=0.79).

Prednisolone Response: 95.12% of MRD-Negative patients responded well compared to 87.50% in MRD-Positive (p=0.30).

Cytogenetics: ETV6/RUNX1 was more frequent in MRD-Negative (9.76%) vs. MRD-Positive (4.17%, p=0.42). BCR/ABL was seen only in MRD-Positive cases (4.17%, p=0.19). MLL was exclusive to MRD-Negative (2.44%, p=0.44).

TLC at Diagnosis: Higher in MRD-Positive (53,597 vs. 37,220, p=0.36). Correlation Between MRD and Outcomes: MRD negativity was strongly linked to better outcomes. Among MRD-Negative patients, 88% were alive and disease-free. In contrast, MRD positivity was predominant in relapsed patients (75%), those undergoing BMT post-relapse (66.67%) and those who relapsed and died (66.67%). Interestingly, 70% of non-relapsed deaths were in MRD-Negative patients, suggesting other contributing factors.

Table 3: Correlation Between Patient Status and MRD Status

Parameter	MRD Negative (n=41)	MRD Positive (n=24)	p-value*
Age			
Mean (years)	5.91	6.40	0.58
Median (years)	5.5	5.75	
Range (years)	0.5-14	0.6-16	
Gender			0.79
Male	20 (48.78%)	13 (54.17%)	
Female	21 (51.22%)	11 (45.83%)	
Prednisolone Response			0.30
Good	39 (95.12%)	21 (87.50%)	
Poor	2 (4.88%)	3 (12.50%)	
Cytogenetics			
Negative	30 (73.17%)	16 (66.67%)	0.57
ETV6/RUNX1	4 (9.76%)	1 (4.17%)	0.42
BCR/ABL	0 (0%)	1 (4.17%)	0.19
MLL	1 (2.44%)	0 (0%)	0.44
TCF3/PBX1	2 (4.88%)	2 (8.33%)	0.57
Not reported	4 (9.76%)	4 (16.67%)	0.42
Karyotype			0.71
NA/Normal	37 (90.24%)	23 (95.83%)	
Hyperdiploid	3 (7.32%)	1 (4.17%)	
Hypodiploid	1 (2.44%)	0 (0%)	
TLC at presentation			
Mean	37,220	53,597	0.36
Median	12,000	16,500	
Range	700 - 216,000	1,100 - 289,900	

Survival Analysis by MRD Status: Kaplan-Meier survival analysis demonstrated superior survival in the MRD-Negative group (n=41) compared to the MRD-Positive group (n=24). MRD-Negative: Survival declined gradually to 80.5% by day 559, maintaining stability until day 2033. (Table 4, Fig. 1)

Table 4: Kaplan-Meier Analysis of Overall Survival by MRD Status in MRD Negative Patients '+'Indicates the last Observed Time Point with no Event

Time (days)	Survival Probability	Events	At Risk
0	1.000	0	41
52	0.976	1	40
132	0.951	1	39
169	0.927	1	38
228	0.902	1	37
286	0.878	1	36
327	0.854	1	35
330	0.829	1	34
559	0.805	1	33
2033+	0.805	0	32

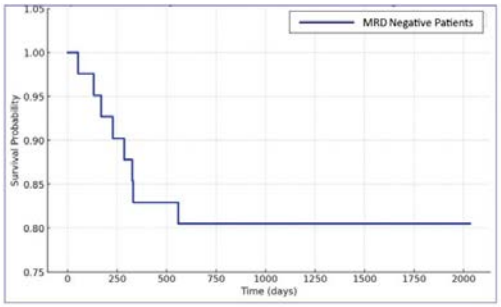

Fig. 1: Kaplan-Meier Analysis Curve of Overall Survival by MRD Status in MRD Negative Patients

MRD-Positive: Rapid decline to 62.5% by day 326, remaining at this level until day 1853. (Table 5, Fig. 2) The survival curves showed a longer plateau for MRD-Negative, indicating better long-term survival, while MRD-Positive patients had an earlier decline. The results emphasize the clinical significance of MRD Negative status as a predictor of improved overall survival.

Table 5: Kaplan-Meier Analysis of Overall Survival by MRD Status in MRD Positive Patients '+' Indicates the last Observed Time Point with no Event

Time (days)	Survival Probability	Events	At Risk
0	1.000	0	24
95	0.958	1	23
154	0.917	1	22
184	0.875	1	21
240	0.833	1	20
265	0.792	1	19
312	0.750	1	18
317	0.708	1	17
321	0.667	1	16
326	0.625	1	15
1853+	0.625	0	14

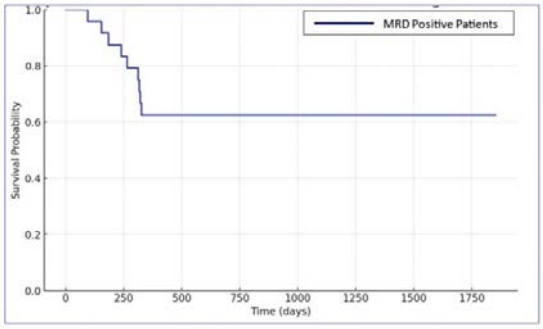

Fig. 2: Kaplan-Meier Analysis Curve of Overall Survival by MRD Status in MRD positive Patient

This study provides valuable insights into the clinicodemographic and prognostic factors influencing survival outcomes in pediatric B-cell acute lymphoblastic leukemia (B-ALL), with a particular focus on minimal residual disease (MRD) as a key prognostic marker. The cohort comprised 65 pediatric B-ALL patients, with a mean age of 6.09 years, predominantly within the 0-5 years age group (53.85%), consistent with Pui[12], who reported a higher incidence of B-ALL in younger children. The gender distribution was nearly equal (50.7% male, 49.3% female), in line with findings from Zhang[13]. At the time of last follow-up, 38.46% of patients were alive and disease-free, 26.2% were still receiving treatment and 15.4% had died, similar to survival trends observed in studies by Vora[6] and Conter[14], where survival was closely linked to MRD status and early treatment response. High total leukocyte count (TLC) at diagnosis (>100,000 in 13.85% of cases), a known poor prognostic indicator Lee[15], was also observed. MRD negativity at the end of induction (63.8%) was strongly associated with improved survival, reinforcing findings by Vora[6] and Conter[14]. The prednisolone response rate was high (92.3%), consistent with Bhojwani[16], who emphasized its prognostic significance in pediatric leukemia. Cytogenetic analysis showed that 7.7% of patients had the ETV6/RUNX1 fusion gene, a favorable prognostic marker as documented by Pui[12]. Karyotyping revealed 92.3% normal chromosomes, with 6.2% hyperdiploid and 1.5% hypodiploid cases, findings that align with Tallen[17], who demonstrated the prognostic impact of chromosomal abnormalities in B-ALL. Kaplan-Meier survival analysis revealed significantly better survival outcomes for MRD-negative patients. By the end of observation, MRD-negative patients had an approximately 18% higher survival probability than MRD-positive patients. These findings align with Vora[6] and Conter[14], who emphasized MRD negativity as a predictor of higher event-free survival (EFS) and overall survival (OS). Although MRD-positive patients were slightly older on average (6.40 years vs. 5.91 years, p=0.58), this difference was not statistically significant. Previous studies by Campana[18] suggest younger patients typically show better MRD clearance, though the interplay between age, genetics and disease biology complicates direct correlations. Prednisolone sensitivity may also contribute to MRD clearance, as 95.12% of MRD-negative patients exhibited a good prednisolone response compared to 87.5% of MRD-positive patients (p=0.30). Although not statistically significant, this trend aligns with Bhojwani[16], who reported that steroid response correlates with better long-term survival. Cytogenetic analysis further supports MRD's prognostic role. ETV6/RUNX1 was more prevalent in MRDnegative patients (9.76%), while BCR/ABL was exclusively found in MRD-positive patients (4.17%), consistent with findings from Pui[12], which indicate that ETV6/RUNX1 is associated with better prognosis, whereas BCR/ABL

predicts poorer outcomes. Similarly, MLL translocations were only found in MRD-negative patients (2.44%), though the small sample size limits statistical conclusions. The role of total leukocyte count (TLC) in prognosis remains complex. While MRD-positive patients had a higher mean TLC (53,597 vs. 37,220, p=0.36), this was not statistically significant. Schrappe[19] suggest that TLC alone is an insufficient prognostic marker but, when combined with MRD and genetic data, provides more robust risk stratification. Our findings reinforce that MRD negativity correlates with improved survival and disease-free status, consistent with extensive research from institutions like the Children's Oncology Group (COG) and St. Jude Children's Research Hospital. While our study was limited by a relatively small sample size, the observed trends align with global literature on MRD as a critical prognostic marker in pediatric ALL.

CONCLUSION

In conclusion, our study highlights the importance of minimal residual disease (MRD) status as a key prognostic factor in pediatric acute lymphoblastic leukemia (ALL). MRD negativity at the end of induction correlates with better overall and disease-free survival, supporting its role as a reliable predictor of outcomes. Although the sample size was small, our findings reinforce the need for early MRD assessment to guide treatment decisions. Larger studies are needed to further explore how other factors, such as genetics and age, influence prognosis in pediatric ALL.

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REFERENCES

1. Berry D.A., S. Zhou, H. Higley, L. Mukundan and S. Fu et al., 2017. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia A Meta-analysis. JAMA Oncol., Vol. 3. 10.1001/jamaoncol.2017.0580.
2. Kantarjian H., N.P. Shah, A. Hochhaus, J. Cortes and S. Shah *et al.,* 2010. Dasatinib versus Imatinib in Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia. New Engl. J. Med., Vol. 362: 10.1056/NEJMoa1002315.
3. Saglio G., D.W. Kim, S. Issaragrisil, P. le Coutre and G. Etienne *et al.,* 2010. Nilotinib versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia. New Engl. J. Med., Vol. 362: 10.1056/NEJMoa0912614.
4. Borowitz M.J., B.L. Wood, M. Devidas, M.L. Loh and E.A. Raetz *et al.,* 2015. Prognostic significance of minimal residual disease in high risk B-ALL: A report from Children's Oncology Group study AALL0232. Blood, Vol. 126: 10.1182/blood-2015-03-633685.
5. Borowitz M.J., M. Devidas, S.P. Hunger, W.P. Bowman and A.J. Carroll *et al.,* 2008. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: A Children's Oncology Group study. Blood, Vol. 111: 10.1182/blood-2008-01-132837.
6. Vora A., N. Goulden, R. Wade, C. Mitchell and J. Hancock *et al.,* 2013. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): A randomised controlled trial. The Lancet Oncol., Vol. 14: 10.1016/S1470 2045(12)70600-9.
7. Das N., S. Banavali, S. Bakhshi, A. Trehan and V. Radhakrishnan *et al.,* 2022. Protocol for ICiCLe-ALL-14 (InPOG-ALL-15-01): A prospective, risk stratified, randomised, multicentre, open label, controlled therapeutic trial for newly diagnosed childhood acute lymphoblastic leukaemia in India. Trials, Vol. 31. 10.1186/s 13063-022-06033-1.
8. Schultz K.R., D.J. Pullen, H.N. Sather, J.J. Shuster and M. Devidas *et al.,* 2007. Risk-and response-based classification of childhood B-precursor acute lymphoblastic leukemia: A combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). Blood, Vol. 109. 10.1182/blood-2006-01-024729.
9. Patel B., L. Rai, G. Buck, S.M. Richards and Y. Mortuza *et al.,* 2010. Minimal residual disease is a significant predictor of treatment failure in non T-lineage adult acute lymphoblastic leukaemia: Final results of the international trial UKALL XII/ECOG2993. Br. J. Haematology, Vol. 148: 10.1111/j.1365-2141.2009.07941.x.
10. Irving J., J. Jesson and P. Virgo, *et al.,* 2009. Establishment and validation of a standard protocol for the detection of minimal residual disease in B lineage childhood acute lymphoblastic leukemia by flow cytometry in a multicenter setting. Haematologica., Vol. 94: 10.3324/haematol.2008.000414.
11. Malec M., V.H.J.V. Velden, E. Björklund, J.M. Wijkhuijs and S. Söderhäll *et al.,* 2004. Analysis of minimal residual disease in childhood acute lymphoblastic leukemia: Comparison between RQ-PCR analysis of Ig/TcR gene rearrangements and multicolor flow cytometric immunophenotyping. Leukemia, Vol. 18: 10.1038/sj.leu.2403444.

12. Pui C.H., L.L. Robison and A.T. Look., 2008. Acute lymphoblastic leukaemia. The Lancet, Vol. 371: 10.1016/S0140-6736(08)60457-2.
13. Zhang X., H. Wu, H. Fan, B. Su, G. Zhang and L. Dong., 2018. Clinical characteristics and prognosis of pediatric patients with B cell acute lymphoblastic leukemia relapse. Oncol. Lett., Vol. 16: 10.3892/ol.2018.8974.
14. Conter V., C.R. Bartram, M.G. Valsecchi, A. Schrauder and R. Panzer-Grümayer *et al.,* 2010. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: Results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood, Vol. 115: 10.1182/blood-2009-10-248146.
15. Lee J.W. and B. Cho., 2017. Prognostic factors and treatment of pediatric acute lymphoblastic leukemia. Korean J. Pediatr., Vol. 60: 10.3345/kjp.2017.60.5.129.
16. Bhojwani D., S.C. Howard and C.H. Pui., 2009. High-Risk Childhood Acute Lymphoblastic Leukemia. Clin. Lymphoma Myeloma, Vol. 9: 10.3816/CLM.2009.s.016.
17. Tallen G., R. Ratei, G. Mann, G. Kaspers and F. Niggli *et al.,* 2010. Long-Term Outcome in Children With Relapsed Acute Lymphoblastic Leukemia After Time-Point and Site-of-Relapse Stratification and Intensified Short-Course Multidrug Chemotherapy: Results of Trial ALL-REZ BFM 90. J. Clin. Oncol., Vol. 28: 10.1200/JCO.2009.25.1983.
18. Campana D., 2012. Minimal residual disease monitoring in childhood acute lymphoblastic leukemia. Curr. Opin. Hematol., Vol. 19: 10.1097/MOH.0b013e3283543d5c.
19. Schrappe M., S.P. Hunger, C.H. Pui, V. Saha and P.S. Gaynon *et al.,* 2012. Outcomes after Induction Failure in Childhood Acute Lymphoblastic Leukemia. New Engl. J. Med., Vol. 366: 10.1056/NEJMoa1110169.