Research Article

# CNS relapse among childhood acute lymphoblastic leukaemia: Experience from a single oncology centre in Baghdad

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## ABSTRACT

**INTRODUCTION**: Relapse of acute lymphoblastic leukaemia (ALL) is the main cause of treatment failure. It may occur at a single extramedullary site or concomitantly with marrow relapse. The central nervous system (CNS) is the most commonly affected extramedullary site in ALL.

**OBJECTIVE**: To determine the percentages of CNS relapse among paediatric patients with ALL and their outcomes and to find any association between relapse and some demo-clinical features who were treated at the oncology unit of the Child's Central Teaching Hospital (CCTH) in Baghdad.

**METHODS**: A retrospective study included a total of 393 children below the age of 15 years who were diagnosed with ALL -LI and -L2 (Precursor B or T cell) type for 6 years from 1st of January 2013 to 31st of December 2018. We enrolled 317 patients in the study. The following parameters were extracted: sex, age at diagnosis, initial peripheral total WBC count, ALL subtype (PB cell and T cell), initial CNS involvement, initial traumatic lumbar puncture, associated clinical findings of CNS relapse, time of CNS relapse and outcome of patients with CNS relapse.

**RESULTS**: Out of 317 patients with ALL who underwent statistical analysis, 20 of them developed CNS relapse (6.3%) and 13 (4.1%) had isolated CNS relapse. The age, gender and ALL subtype had no significant association with risk of CNS relapse in ALL (p-value 0.8, 0.2 and 0.4) respectively, while the initial WBC count, initial CNS involvement, positive traumatic LP are significantly associated with CNS relapse (p 0.03, 0.007, 0.02) respectively. Very early relapse was found in 11 (55%) of patients, while early CNS relapse was seen in 9(45%) of them. Five patients (25%) with CNS relapse were alive while 15 (75%) have died; the mean duration between the time of CNS relapse and the time of death was 3.5 ± 3.04 months. The percentage of survival patients was higher among early CNS relapse patients in comparison to very early relapse patients but statistically not significant (P= 0.09).

**CONCLUSION**: The incidence of CNS relapse in ALL patients was (6.3%) and has a bad prognosis. Leukocyte count > 50 x 109/L at diagnosis, initial CNS involvement, and positive traumatic LP seems to be a significant prognostic factor for CNS relapse in childhood ALL.

**Keywords**: acute lymphoblastic leukaemia, central nervous system relapse, Baghdad.

## INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is the most common malignancy in children.[1] The patients with acute lymphoblastic leukaemia survive longer and longer, with the rates of long time remission of over 80% in children. Therefore, increased attention is given to diagnose and prevent central nervous system (CNS) complications, not only to increase survival, but also to prevent neurological deterioration and the resulting decreased quality of life.[2]

Relapse of ALL is the main cause of treatment failure.[3] It may occur at a single extramedullary site or concomitantly with marrow relapse.[4] The CNS is the most commonly affected extramedullary site in acute lymphoblastic leukaemia[5] with current prophylaxis, less than 10% of ALL patients relapse with CNS disease, but in those identified as good-risk;

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this number decreases to 5%.[6] Some children such as those diagnosed within the first 12 months of life and those with T cell ALL have a higher incidence of CNS leukaemia at diagnosis.[7] Patients with CNS leukaemia, however, which is commonly defined as more than five leukocytes per microliter cerebrospinal fluid (CSF) in the presence of lymphoblasts after cytocentrifugation, suffer from more relapses with CNS involvement and have a significantly poorer outcome compared with CNS-negative patients.[8] CNS disease has been associated with an increased rate of mortality.[9] CNS leukaemia may result from haematogenous spread of circulating leukaemia cells from involved cranial bone marrow through bridging veins to the superficial arachnoids. Haematogenous spread may occur through migration of circulating leukaemia cells through venous endothelium or as a consequence of petechial haemorrhages in case of severe thrombocytopenia.[10]

Risk factors at the diagnosis related to subsequent CNS relapse are T-cell immunophenotype, presence of high-risk cytogenetic abnormalities [t (9;22) and t(4;11)], hyperleukocytosis (above 100x $10^9$/L) and overt CNS leukaemia at diagnosis.[11] The symptoms and signs of clinically overt CNS leukaemia include headache, nausea, vomiting, lethargy, irritability, nuchal rigidity, papilloedema, cranial nerve involvement and hypothalamic syndrome results in hyperphagia, pathologic weight gain, diabetes insipidus, somnolence or behavioural disturbances. Leukaemic subdural involvement and spinal epidural leukaemia with spinal cord compression have been observed.[12] Cerebrospinal fluid findings for the diagnosis of CNS leukaemia require the presence of more than 5 WBCs/$mm^3$, identification of blast cells on cytocentrifuge examination. Treatment directed at the CNS was one of the major advances for improving survival of ALL during the last decades; it consists of intrathecal administration of chemotherapy, high dose systemic chemotherapy and/or cranial radiotherapy.[13]

This study was designed to determine the percentage of CNS relapse among paediatric patients with ALL who were admitted to the oncology unit of the Child's Central Teaching Hospital (CCTH) in Baghdad for 6 years; from 1st of January 2013 to 31st of December 2018. Also to determine their outcome, and to find any association between CNS relapse and some demo-clinical features

## METHODS

**Setting and study design**: A retrospective case series study was conducted in 2019 on records of patients at the oncology unit of the Child's Central Teaching Hospital (CCTH) in Baghdad for 6 years; from 1st of January 2013 to 31st of December 2018.

**Ethical consideration**: The study was conducted in agreement with the recommendations of the Ministry of Health and it was ethically approved by the research committee of the Al-Karkh Health Directorate. Agreement from the administration of the Hospital to use the data was taken and consents were taken from all families for their children to be involved in this study.

**Inclusion criteria**: For sake of this study, ALL was diagnosed when 25% lymphoblast or more were present in the bone marrow. In all patients, diagnosis of lymphoblast was based mainly on standard morphological features of the leukaemic cells; however, in 15 of them, the diagnosis was also made by immunophenotyping study via flow cytometry on peripheral blood/bone marrow aspirate when it was available. Diagnosis of T-cell leukaemia was made either by detecting bone marrow (BM) lymphocytes plus one or more of the following clinical features age >10 years, high initial WBC count, mediastinal widening, or initial CNS involvement. Or by immunophenotyping studies of either peripheral blood or bone marrow when it is available. Initial CNS involvement was diagnosed by detection of blasts cells on CSF cytospin analysis, cranial nerve palsies, or clinical or radiological evidence of leukaemic cells intracranial infiltration. Age and WBC count, have been used to stratify patients at presentation into risk stratification; ***Standard risk*** defined as WBC count less than 50 x $10^9$/L and age (1 - <10 years) and ***High risk*** defined as

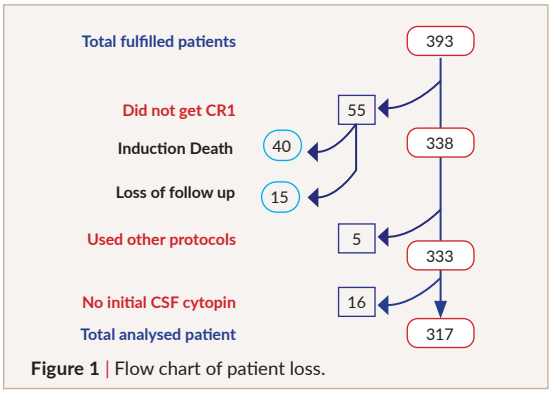


**Figure 1** | Flow chart of patient loss.

WBC count 50 x $10^9$/L or greater at any age or age≥ 10 years or <1 year with any WBC count at presentation.

**Exclusion criteria**: Out of a total of 393 children with ALL, 76 patients were excluded from the study, see figure 1.

**Outcomes**: A total of 317 patients with ALL were evaluated for CNS relapse with a minimum of one year follow up. CNS relapse was diagnosed when patients in 1st complete remission (CR1) had blasts in CSF cytospin analysis with or without clinical evidence of CNS involvement like headache and vomiting, meningeal irritation signs, cranial nerves palsies, seizures and ophthalmological manifestation.

**Procedures and data collection:** The data were collected from record files of the patients and the following parameters were extracted and analysed: sex, age at diagnosis, initial peripheral total WBC count, ALL subtype (Pre-B cell and T cell), initial CNS involvement, initial traumatic LP, associated clinical findings of CNS relapse (e.g., headache, vomiting, meningeal irritation signs, blurred vision, etc.), time of CNS relapse and outcome of patients with CNS relapse.

**Treatment**: We used UKALL protocol-2003 for the treatment of patients; Regimen A for standard risk and regimen B for high risk. Patients with T-cell leukaemia were treated by Berlin-Frankfürt-Münster 95/ T cell Non-Hodgkin Lymphoma/T cell Leukaemia protocol). Patients who had CNS relapse were treated with R3 UKALL protocol 2003 with post-induction cranial irradiation (ALL-R3 consisting of dexamethasone, mitoxantrone, vincristine, L-asparaginase) except one patient who was treated with R3 UKALL and did bone marrow transplantation.

**Definitions:** ***Negative traumatic lumbar puncture (TLP -)*** is defined as red blood cells of ≥ 10/µL with no leukaemic blast cells after cytocentrifugation. While ***positive traumatic lumbar puncture (TLP+)*** is defined as a red blood cell count of ≥ 10/µL with blasts.[14] ***Very Early relapse*** is a relapse that occurs within 18 months of diagnosis. ***Early relapse*** is a relapse that occurs after 18 months of diagnosis but within 6 months of stopping treatment. ***Late relapse*** is a relapse that occurs more than 6 months after stopping treatment.[15]

**Statistical analysis**: was performed using SPSS version 22. The P-value is statistically significant if below (0.05) using Fisher exact test.

## RESULTS

Statistical analysis was done for 317 patients with ALL, 20 of them developed CNS relapse (6.3%). Thirteen patients (4.1%) had isolated CNS relapse while 7(2.2%) developed

**Table 1** | Effect of some demo-clinical parameters on development of CNS relapse in patients with ALL.

| CNS relapse | | Yes (%) | No (%) | p value |
|---|---|---|---|---|
| **Age** | | | | |
| | <1 y | 1(10) | 9(90) | 0.8 |
| | 1-9.9 y | 17(6.3) | 251(93.6) | |
| | ≥10 y | 2(5.1) | 37(94.9) | |
| **Gender** | | | | |
| | Male | 14(7.6) | 170(92.4) | 0.2 |
| | Female | 6(4.5) | 127(95.5) | |
| **Initial WBC** | <50 | 11(4.5) | 229(95.5) | 0.03 |
| | ≥50 | 9(11.6) | 68(88.4) | |
| **ALL subtype** | | | | |
| | PB cell | 18(6) | 277(94) | 0.4 |
| | T cell | 2(9) | 20(91) | |
| **Initial CNS involvement** | | | | |
| Non-traumatic LP+ (17)* | | 4(23.5%) | 13(76.5%) | 0.007 |
| Non-traumatic LP- (272)* | | 11(4.1%) | 261(95.9%) | |
| Traumatic LP+ (9)* | | 4(44.4%) | 5 (55.6%) | 0.02 |
| Traumatic LP- (19)* | | 1(5.3%) | 18 (94.7%) | |

*: The number of patients is written between brackets
**CNS**: Central nervous sytems, **ALL**: Acute lymphoblastic leukaemia, **WBC**: White blood cell, **LP+**: Lumber Puncture positive with leukaemia cells, **LP-**: Lumber puncture negative with leukaemia cells

**Table 2** | Time of relapse from date of diagnosis

| Time of relapse | Number | % |
|---|---|---|
| Very early | 11 | 55 |
| Early | 9 | 45 |
| Total | 20 | 100 |

**Table 3** | Outcome of ALL patients with CNS relapse

| Outcome of Patient with NCS relapse | Number | % |
|---|---|---|
| Alive | 5 | 25 |
| Died | 15 | 75 |
| Total | 20 | 100 |

**Table 4** | Relation of outcome to time of CNS relapse

| Outcome | Total N | Time of relapse | | P value |
|---|---|---|---|---|
| | | Very early N (%) | Early (%) | |
| Alive | 5 | 1 (9) | 4 (44.4) | 0.09 |
| Died | 15 | 10 (91) | 5 (55.6) | |
| Total | 20 | 11 (100) | 9 (100) | |

combined CNS and BM relapse. There is no association between age or gender of patients with the risk of having ALL CNS relapse (p-value 0.8 and 0.2) respectively. Initial WBC, initial CNS involvement, positive traumatic LP are significantly associated with CNS relapse in ALL patients (p-value is 0.03, 0.007, 0.02 respectively), while ALL subtype statistically insignificant risk factor for CNS relapse (p-value is 0.4), as shown in table 1.

The time of CNS relapse from the date of the diagnosis in ALL patients is shown in table 2; 11 of them (55%) had a very early relapse, while 9 of them (45%) had an early CNS relapse. The mean duration ± SD between initial diagnosis of ALL and CNS relapse was 18.3 ± 11.088 months.

The outcome of ALL patients with CNS relapse, 5 of them (25%) are alive while 15 of them (75%) died. The mean duration ± SD between the time of CNS relapse and time of death was 3.5 ± 3.04 months. As shown in table 3.

The percentage of the patients survival with early CNS relapse was higher in comparison to a very early relapse patients but statistically not significant, (P= 0.09). As show in table 4.

## DISCUSSION

In our study, out of 317 children diagnosed as ALL, 20 (6.3%) of them developed CNS relapse and 13 (4.1%) had isolated CNS relapse while 7(2.2%) developed combined CNS and BM relapses. Vilmer E et al,[16] Manera R et al[17] and Xiao P et al[18] found that the risk of isolated CNS relapse was 4.2%, 3.0%, and 4.3%. respectively while the rates of combined CNS and haematological relapses were 8.3% and 6.0%, respectively.[16,17] Similarly, Bürger B et al,[19] Margolin J et al[12] and Der wich K et al[20] reported that CNS relapse is less than 10%. The rate is a bit higher for Saarinen U et al[21] and Cancela CS study[6] who found that Cumulative incidence of CNS relapse was 9.9 ±2% and 11%, while isolated CNS relapse was 4.7 ±1% and 6.8%, respectively. The rate was found to be much higher for Siddiqui EU et al[22], 8 (67%). AL-Shujairi TA et al[23] in a study conducted at our centre has reported that 76 of his patients (23.1%) had CNS relapse; isolated CNS relapse in 42 patients (12.8%) and combined relapse in 34 patients (10.3%). This discrepancy in the result might be explained by the differences in the sample size and the differences in the protocol used in the treatment of patients with ALL; we used dexamethasone in the induction phase instead of prednisolone.

No statistical significance was found between CNS relapse and the age and gender of the patients; a finding which was similar to that of Siddiqui EU et al[22] and Saarinen U et al.[21] However, AL-Shujairi TA et al[23] found that male gender and age below 2 years were significantly associated with CNS relapse, P values are 0.005 and 0.032 respectively; a result that may be linked to the sample size differences.

In the current study, the ALL patients with initial WBC of > 50000/mm$^3$ had a significant risk for CNS relapse, this is comparable to that of AL-Shujairi TA et al[23] and Cancela CS study[6] and Saarinen U et al,[21] however Siddiqui EU et al[22] reported that initial WBC count had no significant association with CNS relapse.

Effect of ALL subtype on development of CVS relapse is variables among studies. We found that it has no statistical significance

similar to the same results of Cancela.[6] However, Saarineen et al[21] have reported that unexpectedly, patients with T-cell ALL did better than those with Precursor-B ALL, Jeha S et al[24] found that children with pre-B acute lymphoblastic leukaemia (ALL) had a significantly higher incidence of CNS relapse, and Pui C-H [25] and Pui C[11] reported that T-cell immunophenotype is a risk factor of CNS relapse. Because of the descriptive nature of our study, it is difficult to state that this difference between the results of our study and that of others might be due to underestimation of T cell leukaemia because of inconsistent availability of flow cytometry in our centre or due to mere intensive therapy that prevents CNS relapse.

In our series a positive traumatic LP is associated with an increased rate of ALL CNS relapse (P=0.02) is consistent with that of Gajjar et al's study.[14] Hafiz MG et al[26] and Bürger B et al[19] has reported that Children with positive traumatic LP status had significantly decreased event-free survival (EFS), 75%, p=0.003, and 73%, P 0.003 respectively. Covington[27] was further supports the importance of taking measures to ensure diagnostic LPs are performed in a controlled setting under general anaesthesia with the highest-level practitioner available. A traumatic tap could introduce circulating blast cells into the CSF or alter the anatomy of the dural space that would affect the delivery of chemotherapy. Anatomical changes to the dural space can affect intrathecal chemotherapy delivery or penetrance and possibly lead to higher rates of CNS relapse. A traumatic spinal tap can also mask CNS disease status.[28]

In this study there was a significant association between initial CNS involvement and CNS relapse this finding is consistent with that of other studies like Bürger B et al,[19] Gajjar A et al,[14] AL-Shujairi TA et al,[23] and Matloub Y et al[29] who reported that Children with ALL who present with CNS disease (CNS3) at diagnosis are at a high risk of CNS relapse.

In this study, 55% of patients had very early CNS relapse while 45% of them had early CNS relapse. The mean duration ± SD between initial diagnosis of ALL and CNS relapse was 18.3 ± 11.088 months. AL-Shujairi et al[23] reported that the mean duration ± SD between diagnosis of ALL and CNS relapse in patients who died or still alive was 10.56±7.27 months versus 20.42±8.50 months, P=0.000041. Siddiqui EU et al[22] reported that the meantime to relapse from diagnosis was 1.3±0.54 years. Masurekar AN et al[30] reported that among 123 ALL patients with CNS relapse, 20 of them had a very early relapse, 71 had an early relapse, and 32 had a late CNS relapse. Barredo JC et al[31] in their study found that out of eight patients with CNS relapse, 5 have a CR1< 18 months, and 3 patients have a CR1>18months.

Unfortunately in our series, the mortality rate among ALL CNS relapse patients was 75%. comparing to ours, Malempati S et al[32] showed better outcome for patients with CNS relapse. This study demonstrated that the patients with early CNS relapse had a high percentage of survival in comparison to very early relapse patients but this difference was statistically none significant, P= 0.09. Whereas a study conducted by Nguyen K et al[33] reported that Five-year survival rates after isolated CNS relapse were as follows: early (N=175): 43.5±4.5%, intermediate (N=180): 68.0±4.6%, (P<0.0001). The relative risk of death for patients with early and intermediate CNS relapses were 3.4-fold and 1.5-fold, respectively.

## CONCLUSION

The incidence of CNS relapse in ALL patients was (6.3%), and still has a very bad prognosis. a leukocyte count > 50 x $10^9$/L at diagnosis, initial CNS involvement, and positive traumatic LP seems to be a statistically significant prognostic factor for increased risk of CNS relapse in childhood acute lymphoblastic leukaemia.

## REFERENCES

1. Horner MJ, Ries LAG, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2006. National Cancer Institute, Bethesda, MD: http://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submission, posted to the SEER Web site, 2009.
2. Van Huynh, Leonard Sender and Daniela A . Acute Lymphoblastic Leukemia: What Have We Learned About the Effects of This Disease and Its Treatment on the Nervous System? .

2011.

3. Gaynon PS. Childhood acute lymphoblastic leukemia and relapse. *Br J Haematol* 2005;131(5):579-87.
4. Pieters R, Carroll WL. Biology and treatment of acute lymphoblasticleukemia. *Hematol Oncol Clin North Am* 2010;24(1):1–18.
5. NÜCKEL, H. et al. Detection of malignant haematopoietic cells in the cerebrospinal fluid by conventional cytology and flow cytometry. *Clin Lab Haem* 2006 ;(28):9-22.
6. Cancela CS. Incidence and risk factors for central nervous system relapse in children and adolescents with acute lymphoblastic leukemia. *Rev Bras Hematol Hemoter*2012;34(6):436-41.
7. Moricke A ,Zimmermann M, Reiter A, et al. Prognostic impact of age in children and adolescents with acute lymphoblastic leukemia: data from trials ALL- BFM 86,90,and 95. *Klin Padiatr* 2005;217:310-320.
8. Pui CH, Boyett JM, Rivera GK, et al. Long-term results of Total Therapy studies 11, 12 and 13A for childhood acute lymphoblastic leukemia at St Jude Children's Research Hospital. *Leukemia* 2000;14:2286-2294.
9. Children's Oncology Group. Treatment of patients with newly diagnosed standard risk b cell lymphoblastic leukemia (B-ALL) or localized b-lineage lymphoblastic lymphoma (B-LLy). Nov 11, 2013.
10. Silverman L and Sallan S. Acute lymphoblastic leukemia. In Hematology of Infancy and Childhood. Sixth edition. Edited by Nathan D, Orkin S, Ginsburg D and Look A. Saunders. pp. 1135-1166
11. Pui CH, Howard SC. Current management and challenges of malignant disease in the CNS in paediatric leukaemia. *Lancet Oncol* 2008 ;9(3):257-68.
12. Margolin J, Steuber C, Poplack D, et al. Acute lymphoblastic leukemia. In Principles and Practice of Pediatric Oncology. Fourth edition. Editted by Pizzo P and Poplack D. Lippincott Williams and Wilkins. Philadelphia 2002: pp. 489-544.
13. Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. *Hematol Oncol Clin North Am*. 2010;24(1):1–18.
14. Gajjar A, Harrison PL, Sandlund JT, et al. Traumatic lumbar puncture at diagnosis adversely affects outcome in childhood acute lymphoblastic leukemia. *Blood* 2000; 96(10):3381-4.
15. Saha Vaskar, Parker C. An international Collaborative Trial for Relapsed Lymphoblastic Leukaemia(ALLR3). Amendment 4 2009; 5.x
16. Vilmer E, Suciu S, Ferster A, et al. Long-term results of three randomized trials in childhood acute lymphoblastic leukemia: CLCG-EORTC report. *Leukemia*. 2000;14:2257-2266.
17. Manera R, Ramirez I, Mullins J, Pinkel D. Pilot studies o species specific chemotherapy of childhood acute lymphoblastic leukemia using genotype and immunophenotype. *Leukemia.* 2000;14:1354-1361.
18. Xiao P, Chai Y, Li J, et al. Therapeutic effectiveness of CCLG-97 protocol on standard-risk childhood acute lymphoblastic leukemia. *Zhonghua Er Ke Za Zhi* 2005; 43(7): 486-489.
19. Bürger B, Zimmermann M, Mann G, et al. Diagnostic cerebrospinal fluid examination in children with acute lymphoblastic leukemia: significance of low leukocyte counts with blasts or traumatic lumbar puncture. *J Clin Oncol* 2003; 21(2):184-1
20. Derwich K, Kaczmarek M, Wachowiak J, et al. Treatment results in children with standard-risk acute lymphoblastic leukemia. Report of the Polish Pediatric Leukemia/Lymphoma study group. *Rev Prat* 2004; 61(2): 49-52.
21. Saarinen U, Gustafson G, Carlsen N, et al. Outcome of children with high-risk acute lymphoblastic leukemia: Nordic results on an intensive regimen with restricted central nervous system irradiation. *Pediatr Blood Cancer* 2004; 42(1): 8-23.
22. Siddiqui EU, Kazi SG, Habib MI, et al. Pattern of relapse in paediatric acute lymphoblastic leukaemia in a tertiary care unit . *J Pak Med Assoc* 2016;66(8):961-967.
23. AL-Shujairi TA, Alnassir IJ, Abbas AA, et al. Central nervous relapse in acute lymphoblastic leukemia: prognostic factors and the outcome. *The Iraqi postgraduate medical journal* 2008; 7(4): 339-342.
24. Jeha S. New therapeutic strategies in acute lymphoblastic leukemia. *Semin Hematol* 2009; 46(1): 76-88.
25. Pui C-H. Toward optimal central nervous system-directed treatment in childhood acute lymphoblastic leukemia. *J Clin Oncol.* 2003;21:179-181.
26. Hafiz MG, Jamal CY, Islam A et al. Prognostic Significance of Cerebrospinal Fluid Lymphoblasts at Initial Presentation with Acute Lymphoblastic Leukemia Attending at Bangabandhu Sheikh Mujib Medical University, Bangladesh. *Journal of Pediatrics and Neonatal Care* 2017; 6(2): 00240.
27. Covington G. Traumatic Initial Lumbar Punctures in Childhood Acute Lymphoblastic Leukemia: Predictive Factors and Impact on Disease Outcome. A Clinical Quality Improvement Study. UNC Eshelman School of Pharmacy 2016.
28. Dao JQ 1, Khatua S, Rytting ME, et al. Hydrocephalus as Clinical Indicator of Central Nervous System Relapse in Acute Lymphoblastic Leukemia. *Progressive Science* 2015; 2(3):1-4.
29. Matloub Y, Bostrom BC, Hunger SP, et al. Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood* 2011; 118(2): 243-251.
30. Masurekar AN, Parker CA, Shanyinde M, et al. Outcome of Central Nervous System Relapses In Childhood Acute Lymphoblastic Leukaemia – Prospective Open Cohort Analyses of the ALLR3 Trial. *PLoS One*. 2014; 9(10): e108107.
31. Barredo JC, Devidas M, Lauer SJ, et al. Isolated CNS Relapse of Acute Lymphoblastic Leukemia Treated With Intensive Systemic Chemotherapy and Delayed CNS Radiation: A Pediatric Oncology Group Study. *J Clin Oncol* 2006; 24:3142-3149.
32. Malempati S, Gaynon PS, Sather H, et al. Outcome After Relapse Among Children With Standard- Risk Acute Lymphoblastic Leukemia: Children's Oncology Group Study CCG-1952. *J Clin Oncol*. 2007;25(36):5800-7.
33. Nguyen k, Devidas M, Cheng SC, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: A Children's Oncology Group study. *Leukemia* 2008; 22: 2142–2150.

**Abbreviations list**: 1st complete remission (**CR1**), Acute lymphoblastic leukaemia (**ALL**), Bone marrow (**BM**), Central nervous system (**CNS**), Cerebrospinal fluid (**CSF**), Child's Central Teaching Hospital (**CCTH**), Cubic Millilitre (**mm3**), Event free survival (**EFS**), Negative traumatic lumbar puncture (**TLP -**), positive traumatic lumbar puncture (**TLP+**), Standard Deviation (**SD**), Statistical Package for the social science (**SPSS**), White blood cells (**WBCs**).

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