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"The Risk Factors Associated With The Development Of Tumour Lysis SyndromeIn Children With Acute Lymphoblastic Leukemia"

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Abstract
Introduction: *Acute lymphoblastic leukemia is the most common childhood hematological malignancy. Tumor lysis syndrome is one of the most frequent life-threatening oncological emergencies of childhood Acute lymphoblastic leukemia characterized by metabolic abnormalities including hyperuricemia, hyperphosphatasemia, hyperkalemia, hypocalcemia and azotemia that occur spontaneously 3 days before or within 7 days after initiation of induction chemotherapy.The aim of this study was to identify the risk factors associated with the development of tumour lysis syndrome in children with acute lymphoblastic leukemia.*
Methods:*This was a prospective observational study and was conducted in the Department of Pediatric Hematology and Oncology of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh during the period from November 2017 to October 2018. In our study, we included diagnosed cases of ALL who were admitted to the Department of Pediatric Hematology and Oncology during the study period.*
Result:*Out of 80 patients, rate of tumor lysis syndrome was encountered in 12.5% patients. Among them 60% patients developed spontaneous tumor lysis syndrome while other 40% developed tumor lysis syndrome within 7 days after initiation of induction chemotherapy. In this study age, sex, initial LDH, mediastinal mass, immune phenotype, treatment regimen was not considered as risk factor. Only initial high White Blood Cell count was considered as strong risk factor. All the 10 patients fulfilled the criteria of laboratory tumor lysis syndrome and no one had clinical tumor lysis syndrome.*
Conclusion:*In this study, rate of tumor lysis syndrome was found to be 12.5%. Occurance of spontaneous tumor lysis syndrome was greater than that occurred within 7 days after initiation of chemotherapy. No patient had developed clinical tumor lysis syndrome. Initial high white blood cell count was found to be a strong predictor for the development of tumor lysis syndrome.*

Keywords:*Acute Lymphoblastic Leukemia,Tumour Lysis Syndrome,Risk Factors*

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I. Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. It represents 25%-30% of all childhood cancer & approximately 75% of all cases of childhood leukemia.[1] At our center, in the Department of Paediatric Haematology and Oncology of BSMMU, 58% of cases of ALL among 455 newly diagnosed children with malignancy were recorded in one year.[2] The use of effective polychemotherapy

protocols in the last 3 decades and precise supportive care has determined a steady improvement of outcomes in children with ALL. This is why ALL is now considered a curable disease in children. [3] Tumor lysis syndrome is a group of metabolic abnormalities consisting of hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and azotemia resulting from the rapid release of intracellular metabolites such as nucleic acids, proteins, phosphorus, and potassium from lysed malignant cells.[4] This process can potentially cause acute renal failure, arrhythmias, seizures, and even death. Tumor lysis syndrome can occur spontaneously before or within 12-72 hours after initiation of cytoreductive chemotherapy for malignancies.[5,6] TLS is most frequently associated with hematological malignancies such as AML and ALL as well as NHL, particularly Burkitt lymphoma, and requires prompt recognition followed by aggressive management.[7-9] It is essential to identify patients at risk of tumor lysis syndrome because this life-threatening condition may occur rapidly and is preventable. Tumor lysis syndrome risk derives from the collective contribution of several individual risk factors. It underlines the critical need for a risk model that integrates them in order to identify high risk, even in unusual settings. Risk factors include age, type of malignancy, presentation with a high initial WBC count, evidence of large tumor burden (hepatosplenomegaly), high blood LDH or increased serum uric acid level, pre-existing dehydration, oliguria, renal failure; and malignancies with high chemosensitivity. [10-14] Other studies have reported unexpected cases of TLS where a high TLS risk was not evident and for which appropriate risk assessment and management could make the difference between life and death.[15,16] Complications resulting from TLS, can compromise the efficacy or further administration of chemotherapy and impact morbidity and mortality.[17,18] They are also associated with longer and costlier hospital stays.[19,20] Previous studies focused primarily on identifying patients at increased risk of TLS for the purpose of selecting those who may benefit from increased laboratory monitoring or urate oxidase therapy.[21,22] However, the majority of children with newly diagnosed ALL who are treated with standard TLS prophylactic measures do not experience, clinically significant laboratory abnormalities either before or shortly after chemotherapy.[5] Precise and uniform criteria for defining TLS described by Cairo and]Bishop in 2004 are accepted universally. [23]

Objective of the study

The main objective of the study was to identify the risk factors associated with the development of tumour lysis syndrome in children with acute lymphoblastic leukemia.

II. Methodology & Materials

This was a prospective observational study and was conducted in the Department of Pediatric Hematology and Oncology of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh during the period from November 2017 to October 2018. In our study, we included diagnosed cases of ALL who were admitted to the Department of Pediatric Hematology and Oncology during the study period.

These are the following criteria to be eligible for enrollment as our study participants: a) Patients aged 1 to 18 years; b)Patients newly diagnosed with ALL; c) Patients admitted in the department; d) Patientswith pretreatment and within 7 days after initiation of induction chemotherapy; e) Patients who were willing to participate were included in the study And a) Patients with known case epilepsy and other convulsive disorder; b) Patients withaknown case of congenital heart diseases; c) Patients with previous surgical history; d) Patients with any history of acute illness (e.g.,renal or pancreatic diseases) were excluded from our study.

Study procedure: Chemotherapy was given to all patients with acute lymphoblastic leukemia according to UKALL 2003 protocol after stratifying risk. Regimen-A was given to standard risk group and regimen-B was specified for high risk group as there was no facility for giving Regimen C. Induction phase is the first phase of the protocol, which comprises of 35 days. In case of regimen A, the chemotherapeutic agent used in induction phase includes oral dexamethasone (dose:6-10mg/m2, on Day 1-35), vincristine (dose: 1.5mg/m2, IV on Day 2, 9, 16, 23 and 30), L-asparaginase (dose: 6,000 I.U/m2,IM on Day 4,6,8,10,12,14,16,18,20) ,6-mercaptopurine (75mg/m2 on Day 28-35),and IT/ TIT (intrathecal methotrexate, hydrocortisone and/or cytosine-arabinoside). However, in regimen-B another drug daunorubicin (25mg/m2 on Day 2, 9, 16 and 23) is given additionally. General supportive management like hydration, alkalinization, allopurinol, phosphate binder, oral care, anal care etc was administered in all patients. Patients was on regular follow upto completion of induction chemotherapy. Blood biochemistry like S.Inorganic PO4, S.Uric acid, S.Creatinine, S. Electrolytes was measured daily if tumor lysis occur 3 days before or within 7 days after initiation of induction chemotherapy. In some patients with very higher count follow was done for two to three days more. Clinical information about urine output, oliguria, anuria, periorbital edema, leg edema, ascites, blood pressure, heart rate, pulse rate, cough, breathlessness, tetany, seizure, unconsciousness was followed up daily 3 days before and within 7 days after initiation of induction chemotherapy. S.Uric acid, S.Calcium and S.Creatinine was measured by auto analyzer (Humalyzer 3000,USA or Photometer 5010 v5+,Germany) in our department. Serum samples needed for measurement of s.creatinine, S.Uric acid and S.Ca are 100 microlitre, 25 microlitre and 10 microlitre respectively. Time requirement for getting the results are 1.5 min, 10 min and 15

min respectively. S.Electrolytes was measured by auto analyzer (Biolyte 2000).[24] 40 microliter serum was taken after centrifugation of 3ml patient blood. Standard A&B reagents, cleaning solution and conditioning solution was added. The test took 1 min to give result. S.Inorganic PO4 was measured by auto analyzer (Dimension by SIEMENS,USA) in biochemistry department. 3 microliter serum sample was taken and 50 microliter reagent 1, 20 microliter reagent 2 and 20 microliter reagent 3 was added.

Statistical Analysis: All data were recorded systematically in preformed data collection form and quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. Statistical analysis was performed by using SPSS 21 (Statistical Package for Social Sciences) for Windows version 10. Probability value <0.05 was considered as level of significance. The ethical Review Committee of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh approved the study.

III. Results

Table 1: Demographic characteristics of the study subjects (N=80)

Demographiccharacteristics	Frequency	Percentage (%)
Age		
<10 years	65	81.3
>10 years	15	18.8
Sex		
Male	51	63.8
Female	29	36.3
WBC		
<50000/cumm	60	75.0
>50000/cumm	20	25.0
LDH		
<1000U/L	42	52.5
>1000U/L	38	47.5
Mediastinalmass	6	7.5
ALL		
B	72	90.0
T	8	10.0
Treatmentregimen		
A	49	61.3
B	31	38.8
Rateoftumour lysis		
Positive	10	12.5
Negative	70	87.5

Table1showsthedemographiccharacteristicsofthestudypopulation.81.3% of patientsare <10 years of age, 63.8% are male, and 75% have IC <50000/cumm. Among the patients, 52.5% have initial LDH<1000U/L, 6(7.5%) presented with mediastinal mass, 90% of patients are B cell origin, and 61.3% were treated with Regimen A. Among the patients, 12.5%have TLS.

Table 2: Associationofparametersintumourlysissyndrome

Parameters	Tumourlysissyndrome				P-value
	Positive		Negative		
	N	P(%)	N	P(%)	
Age					
1-10 years	7	70	58	82.9	0.330
>10 years	3	30	12	17.1	
Gender					
Male	4	40	47	67.1	0.095
Female	6	60	23	32.9	
Initial WBC					
< 50000/cumm	4	40	56	80	0.006
> 50000/cumm	6	60	14	20	
Initial LDH					

< 1000U/L	3	30	39	55.7	0.128
> 1000U/L	7	70	31	44.3	
Mediastinal mass					
Yes	2	20	4	5.7	0.109
No	8	80	66	94.3	
ALL immunophenotype	**8**	**80**	**64**	**91.4**	**0.260**
B cell	**2**	**20**	**6**	**8.6**	
T cell					
Treatment regimen					
A	**2**	50	47	67.1	0.481
B	2	50	23	32.9	

Table 2 shows the association of parameters in TLS of the study population. Among the 10 TLS-positive patients 70% of patients are within the 1-10 years age group and 30% are >10 years old. Among the 10 TLS positive patients 40% patients are male and 60% are female. Among TLSpositivepatients40%patientshaveinitialWBCcount<50000/cummand60% have initial WBC count >50000/cumm and 30% patients have initial LDH <1000U/L and 70% have initial LDH >1000U/L. Among all TLS positive patients, 20% patients have mediastinal mass and 80% are B cell origin and 20% are T cell origin. Among the 4 TLS positive patients 50% are treated with regimen A and 50% are treated with regimen B.

Table 3: Prevalenceoflaboratoryabnormalitiesinpatientswithchildhood acute lymphoblastic leukemia

Laboratoryparameter	**Frequency**	**Percentage(%)**
Hypocalcemia	12	15.0
Hyperuricemia	7	8.8
Hyperphosphatemia	12	15.0
Hyperkalemia	0	0.0
Azotemia	3	3.8
Hypocalcemiaand hyperuricemia	2	2.5
Hypocalcemia and hyperphosphatemia	6	7.5
Hyperphosphatemiaand hyperuricemia	2	2.5
Hyperkalemiaand hypocalcemia	0	0.0
Hyperkalemiaand hyperuricemia	0	0.0
Hyperkalemia and hyperphosphatemia	0	0.0
Hypocalcemiaand azotemia	2	2.5
Hyperphosphatemiaand azotemia	0	0.0
Hyperuricemiaand azotemia	0	0.0
Hyperkalemiaand azotemia	0	0.0

Table 3 demonstrates the prevalence of lab parameters of TLS including hypocalcemia and hyperphosphatemia both were 15%, hyperuricemia was 8.8%, azotemia was 3.8% and hypocalcemia and hyperphosphatemia was 7.5% in our study.

Table 4: Regression analysis for risk factors assessment

Variables	**B**	**S.E.**	**P-value**	**OR**	**95%CI**	
					Lower	**Upper**
WBC(>50000/cumm)	.112	1.117	.042	1.119	.125	9.986
Treatmentregimen(B)	1.836	1.367	.179	6.269	.430	91.369
Age(<10yrs)	.618	1.040	.552	1.855	.242	14.236
Sex(female)	1.923	.946	.920	6.843	1.071	43.730
LDH (>1000U/L)	1.048	.842	.213	2.853	.547	14.871
M Mass (no)	-.960	1.786	.591	.383	.012	12.674
ALL (B)	.161	1.714	.925	1.174	.041	33.770

Table 4 shows the regression analysis of the risk factors for the development of TLS which showed that only initial WBC value> 50000/cumm is the strong risk factor for the development of TLS in childhood acute

lymphoblastic leukemia. Other predictors of TLS like age, sex, initial LDH, immunophenotype, mediastinal mass, and treatment regimen regarding acute childhood lymphoblastic leukemia showed no statistical significance.

IV. Discussion

Acute lymphoblastic leukemia (ALL) is the most common malignancy in the pediatric age group accounting for one-fourth of all childhood cancers. Last few years the cure rate of ALL is surprisingly high due to the development of supportive care.

The rate of TLS in this study is 12.5%. This finding correlates with the incidence of TLS ranging from 3% to 22%.[25] According to Truong H T et al., the prevalence of TLS in children with ALL before and within 1 week of chemotherapy initiation was 23%. [26] According to Bagshi M A et al.,TLS occurs in a high percentage of children with ALL (19%), even prior to chemotherapy (4%).[27] In a previous study high incidence of 45% incidence of developing TLS was reported in children with acute lymphoblastic leukemia.[28]

Truong H T et al. showed that patients whose age > 10 years developed TLS significantly (P value <0.0001).[26] Abdel-Baset H A et al., did not find significant relation regarding the development of TLS with age >10 years (P value 0.2). [29] In this study age > 10 years is not a significant risk factor for the development of TLS (P value 0.330).

Male sex is not a significant risk factor for the development of TLS in this study (P value 0.095) which is comparable with the finding of Abdel-Baset H A et al., and Saeed F et al., that male sex is not a risk factor for development of TLS (P value 0.08). [29,30] Bagshi M A et al., found significant relation of male sex with TLS (P value <0.001).[27]

In this study,an initial WBC count > 50000/ cumm is significant with the development of TLS in childhood ALL (P value 0.006). This is also consistent with the result of Bagshi M A et al.,that WBC count >50000 is a significant risk factor for the development of TLS (P value <0.0001).[27]A prospective observational study conducted in BSMMU by Tasmeen R et al.,found that TLS developed in 26% with WBC count below one lac, 50% with WBC count of 1 lac to 2 lacs, and increased upto 100% with WBC count > 3 lacs.[31]

Abdel-Baset H A et al., found a significant relation of initial LDH >1000 U with development of TLS (P value 0.02).[29] Patients with high LDH had a higher incidence of TLS and there was a strong association between TLS development and high initial LDH.[28] But in this study, initial LDH > 1000 is not a statistically significant risk factor for the development of TLS (P value 0.128).

Among the 26 patients presented with mediastinal mass out of 328 patients in a study conducted by Truong T H et al.,found that 19 patients developed TLS (OR 12.2, 95% CI 4.9-30.4, P value < 0.0001).[26] No statistical significance was found with mediastinal mass to TLS (P value 0.109) in this study. This may be due to the use of effective supportive treatment.

T cell immunophenotype is not significantly associated with the development of TLS in this study (P value 0.260). Truong T H et al., showed that there was a strong association between T cell immunophenotype and development of TLS (OR 8.2, 95% CI 4-17, P value <.0001). [26] Another study conducted by Abdel-Baset H A et al., made a significant association with both B and T cell immunophenotypes to the development of TLS (OR 0.1, 95% CI 0.03-0.5, P value 0.002 and OR 8, 95% CI1.9- 32.7, P value <0.002 respectively). [29] According to Wilson and Berns 2014, TLS is significantly associated with B cell ALL.[32] In a study by Wössmann et al., 1791 children with B-precursor ALL had the highest risk to develop TLS (26.4%).[33]

A retrospective study conducted by Truong T H et al., with a large study population of 328 found that 171(52.1%) patients were treated with 3 drug induction chemotherapy protocol, while 136(41.5%) patients were treated with 4 drug induction chemotherapy protocol.[26] But there was no statistically significant variation comparing the development of TLS. In this current study, 49(66.2%) patients are treated with Regimen A(3 drug induction) chemotherapy, while 25(33.7%) patients are treated with Regimen B(4 drug induction) chemotherapy. No significant association is found between Regimen A and Regimen B chemotherapy.

Hypocalcemia and hyperphosphatemia are the most frequent laboratory abnormalities in this study. The frequency of both parameters is 12 and the prevalence rate is 15%. The second most frequent parameter is hyperuricemia 7(8.8%). Hypocalcemia was the most frequent laboratory abnormality in several international studies. A retrospective study regarding TLS in childhood acute lymphoblastic leukemia was performed in Toronto, Canada with a study population of 328. Among them, 148(45.1%) patients had hypocalcemia which was the most prevalent laboratory abnormality.[26] Another retrospective review study of 60 patients also demonstrated the highest prevalence of hypocalcemia.The second most common laboratory abnormality was hyperuricemia in the above-reported studies.[29]

The most common laboratory abnormality pair for TLS is hypocalcemia and hyperphosphatemia (6 of 80 patients 7.5%), followed by equal frequencies of hypocalcemiaandhyperuricemia,hyperphosphatemiaandhyperuricemia, hypocalcemia and azotemia 2(2.5%). A

cross-sectional analytical study of 160 ALL patients demonstrated that the most prevalent laboratory abnormality pair for TLS was hypocalcemia and hyperphosphatemia (10 of 160 patients; 6.25%), followed by concurrent abnormalities of hypocalcemia and hyperuricemia (5.6%).[34]

The results of regression analysis of the risk factors for the development of TLS showed that only the initial WBC value>50000/cumm is the strong risk factor for the development of TLS in childhood acute lymphoblastic leukemia (P value 0.042). Other predictors of TLS like age, sex, initial LDH, immunophenotype, mediastinal mass, and treatment regimen regarding acute childhood lymphoblastic leukemia showed no statistical significance.

Although many studies showed diversity in the rate of development of TLS in patients with childhood ALL, the present study findings are quite similar to some of them. Initial WBC count>50000U/L per cumm of blood is associated with the development of childhood acute lymphoblastic leukemia and is statistically significant in univariate analysis. Patients with age<10 years, B cell lineage ALL, treatment regimen B absence of mediastinal mass, initial WBC count>50000U/L, initial LDH >1000U/L at diagnosis had a higher percentage of development of TLS; which also was identified in various studies. On the contrary, male sex, age >10 years, presence of mediastinal mass, initial LDH>1000U/L, and T cell immunophenotype have been found as risk factors in various studies. In this study, all the TLS-positive patients fulfilled the criteria of TLS, while no patients developed clinical tumor lysis syndrome(CTLS).

V. Limitations of the study

Our study was a single-centre study. We took a small sample size due to our short study period. After evaluating those patients, we did not follow them up for the long term and have not known other possible interference that may happen in the long term with these patients.

VI. Conclusion and recommendations

In our study, we found the rate of development of tumor lysis syndrome in childhood acute lymphoblastic leukemia was 12.5%. The frequency of tumor lysis syndrome was higher in 3 days before starting induction chemotherapy. No patient developed clinical tumor lysis syndrome which could be due to the use of effective supportive treatment and meticulous follow-up. High white blood cell count at presentation had a strong association with the development of childhood Acute lymphoblastic leukemia.

So further study with a prospective and longitudinal study design including a larger sample size should be conductedfor better understanding and management regarding TLS.

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