IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 4 Ser.9 (April. 2022), PP 09-14
www.iosrjournals.org

Tumor Lysis Syndrome: Incidence and Pathogenesis in a Single Centre Study

Dr. Tanjina Afrin[1], Professor Dr. A B M Yunus[2], Professor Dr. Abdul Aziz[3], Professor Dr. Salahuddin Shah[4], Dr. Md. Adnan Hasan Masud[5], Dr. Kazi Md Kamrul Islam[6] Dr. Shamim Reza[7], Dr. Shahidul Islam[8]

[1]*Consultant, Department of Haematology, Green view clinic, Dhaka, Bangladesh*
[2]*Professor, Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh*
[3]*Professor, Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh*
[4]*Chairman, Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh*
[5]*Consultant, Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh*
[6]*Medical Officer, Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh*
[7]*Resident, Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh*
[8]*Lieutenant Colonel, Department of Haematology, Combined Military Hospital (CMH) Barishal, Bangladesh.*
Corresponding author: Dr. Tanjina Afrin

Abstract
Introduction: *Tumor lysis syndrome (TLS) is a life-threatening problem with high morbidity which normally can occur due to the treatment of hematological malignancies or sometimes as solid tumors. Basically, TLS occurs as per the rapid devastation of tumor cells due to cancer chemotherapy initiation and spontaneously in one-third of the cases. The aim of the study was to determine the frequency of TLS in patients with Acute Lymphoblastic Leukemia (ALL).* ***Methodology:*** *This observational cross-sectional study was conducted in the Department of Hematology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh. A total 60 patients were selected for this study. Data was analyzed by computer with the help of SPSS version 21 (Statistical Package for the Social Sciences) version-20 and MS-Excel 2016.* ***Results:*** *There were 32(53.33%) respondents from <20 years which was the highest participation and the Mean age was 30years, where female was 41(68.33%) and male was 19(31.67%). Fever was found in 60(100.00%). Bony tenderness was found in 35(58.33%) and followed by Splenomegaly in 29(48.33%), Lymphadenopathy in 28(46.67%), Oral ulcer in 28(46.67%), Hepatomegaly in 22(36.67%). Total WBC count (x109/L) was (6-435) and the Mean±SD was 52.51±78.70 and followed by Hb% (gm/dl) was (4.1-13.4) and 9.25±1.49, Platelet (x109/L) was (5-20000) and 505.20±2815.29. Blast in PBF (%) was (Oct-90) and 53.80±21.251. S. LDH (U/L) was (198-11863) and 1591.53±2195.47. S. uric acid (mg/dL) was (1.40-30.03) and 5.76±4.61. B Cell was in 38(63.33%) and T Cell was in 22(36.67%) cases. clinical TLS was in 6(33.33%) and Lab TLS was in 12(66.67%).* ***Conclusion:*** *The incidence of TLS is increasing because of more effective cancer treatments in recent years and hence it is required to pay due attention in this matter.*

Keywords: *Tumor Lysis Syndrome, Incidence, Pathogenesis*

Date of Submission: 05-04-2022 Date of Acceptance: 20-04-2022

I. Introduction:

Tumor lysis syndrome (TLS) is a life-threatening problem with high morbidity which normally can occur due to the treatment of hematological malignancies or sometimes as solid tumors.[1] Basically, TLS occurs as per the rapid devastation of tumor cells due to cancer chemotherapy initiation and spontaneously in one-third of the cases.[2,3] TLS has the characteristics of the rapid increase of intracellular contents along with 25% subsequent change in above or below average level and also for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy.[4,5] The laboratory TLS was found in about 40% adults with hematologic malignancies and even up to 70% of children with acute leukemia and clinical form in <10% in a study from 90s.[6-10] This initial knowledge caused a remarkable reduction in the incidence of TLS through the development of strict preventive measures and step-wise dosing and therapeutic sequencing strategies.[11] Although the incidence of clinically significant TLS was only 6%, in a retrospective study the incidence of TLS was reported to be 42% and also it had been reported as most commonly in acute lymphoblastic leukaemia and high-grade NHL, in particular Burkitt's lymphoma.[8] It

was also claimed that TLS can occur in solid tumours with high proliferative rates and a high response rate to cytotoxic therapy, for example, testicular cancer, breast cancer and small cell lung cancer. When tumor cells die, intracellular stuffs are quickly unconstrained into the systemic circulation. As the most plentiful cation within cells is potassium and the most abundant anion is phosphate, this results tumor cell lysis to rapidly follow the hyperkalemia and hyperphosphatemia. The Uric acid may cause acute kidney injury through intrarenal crystallization and also by the crystal-independent mechanisms, like renal vaso-constriction, impaired autoregulation, decreased renal blood flow, oxidation, and inflammation.[12-14] TLS can also cause cytokines which results in a systemic provocative response syndrome and aslo multiorgan failure.[15-17] The purpose of this study was to determine the frequency of TLS in patients with Acute Lymphoblastic Leukemia (ALL).

II. Objective

General

• To observe the frequency of Tumor lysis syndrome in patients with Acute Lymphoblastic Leukemia.

Specific

• To observe the frequency of spontaneous tumor lysis syndrome

• To observe the frequency of therapy related tumor lysis syndrome

III. Materials & Methodology

This observational cross-sectional study was conducted in the Department of Hematology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh. Newly diagnosed case of Acute Lymphoblastic Leukemia patients admitted in the department of Hematology in BSMMU, Dhaka during the study period. For this study there followed consecutive sampling method. The duration of the study was 12 months and included 73 number of Acute Lymphoblastic Leukemia patient who had attained in in-patient or out-patient department of Haematology in BSMMU meeting the inclusion & exclusion criteria. The aim, benefit and the likely risk was explained to the patient if he/she agree then informed written consent was taken.

Inclusion criteria:

All newly diagnosed Acute Lymphoblastic Leukemia patients on the basis of CBC with PBF, bone marrow study and immunophenotyping

Exclusion criteria:

• Relapsed and secondary case of Acute Lymphoblastic Leukemia

• Known case of epilepsy and other convulsive disorder

• Known case of chronic kidney disease

A total 60 patients were selected for this study. Clinical history was taken and physical examination (Anemia, Dehydration, Lymphadenopathy, Purpuric rash, Organomegaly, seizure, oliguria, oedema) was evaluated. Baseline electrocardiography of each patient was recorded at presentation and was repeated if patient developed any symptoms or noticed to have arrhythmia. All the documents necessary to confirm the diagnosis were collected. Venous blood samples were drawn in EDTA tube for total leucocyte count (TLC) and were analyzed on Sysmex analyzer. Venous blood samples were drawn in lithium heparin coated vacutainers to determine the levels of serum phosphate, potassium, uric acid, creatinine, calcium, albumin and serum lactate dehydrogenase (LDH) at presentation and then were checked daily from 3 days before and 7 days after initiation of chemotherapy. These samples were run on NOVA biomedical-4 automated analyzer for serum potassium and on Hitachi 911 automatic analyzer for serum uric acid, creatinine, calcium, phosphate, albumin and LDH. Qualitative variables (eg. sex) of this study were expressed as percentage. Quantitative variables (eg. age) were expressed as mean ± standard deviation. Categorical comparisons were performed using chi-square test. Numerical variables were presented as mean, median and standard deviation. Data was analyzed by computer with the help of SPSS version 21 (Statistical Package for the Social Sciences) version-20 and MS-Excel 2016.

IV. Results

This study was a hospital-based, cross sectional descriptive observational study and was conducted in the Departments of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka. Table-1 shows the age distribution of the study people. There were 32(53.33%) respondents from <20 years and followed by 15(25.00%) from 21-29 years, 7(11.67%) from 30-39 years, 6(10.00%) from ≥40 years. The Mean age was 30±10.42. Figure-1 shows the gender distribution of the study people where male was 41(68.33%) and female was 19(31.67%). Table-2 represents the distribution of the study people according to the following symptoms where Fever was found in 60(100.00%) cases and followed by Progressive pallor in 58(96.67%), History of blood transfusion in 21(35.00%), Bleeding manifestation in 17(28.33%), Palpitation in 2(3.33%) and Convulsion in 1(1.67%).Table-3 shows the clinical findings of the study patients' Bony tenderness was found in

35(58.33%) and followed by Splenomegaly in 29(48.33%), Lymphadenopathy in 28(46.67%), Oral ulcer in 28(46.67%), Hepatomegaly in 22(36.67%), Distended abdomen in 6(10.00%), Oliguria in 5(8.33%), Leg oedema in 5(8.33%), Ascitis in 3(5.00%), Basal Crepitation in 3(5.00%), Jaundice in 2(3.33%), Haematuria in 1(1.67%) and Facial Oedema in 1(1.67%). Table-4 shows the biological feature of the study patients. The range of Total WBC count (x109/L) was (6-435) and the Mean±SD was 52.51±78.70 and followed by Hb% (gm/dl) was (4.1-13.4) and 9.25±1.49, Platelet (x109/L) was (5-20000) and 505.20±2815.29. Blast in PBF (%) was (Oct-90) and 53.80±21.251. S. LDH (U/L) was (198-11863) and 1591.53±2195.47. S. uric acid (mg/dL) was (1.40-30.03) and 5.76±4.61. S. inorganic phosphate (mg/dL) was (2.30-7.70) and 4.19±1.20. S. potassium (mmol/L) (2.50-5.40) and 3.92±0.56. S. calcium (mg/dL) was (1.10-11.80) and 8.33±2.08. S. creatinine (mg/dL) was (0.19-3.59) and 89±0.55. Figure-2 shows the immunophenotyping of ALL patients where B Cell was in 38(63.33%) and T Cell was in 22(36.67%) cases. Figure-3 shows the prevalence of TLS among all patients and among them 71% were absent and 29% were present. Figure-4 shows the distribution of lab and clinical TLS among TLS patients where clinical TLS was in 6(33.33%) and Lab TLS was in 12(66.67%). Figure-5 shows the distribution of TLS according to onset where therapy related TLS was in 7(41.18%) and spontaneous TLS was in 11(58.82%) cases.

Table-1: Age distribution of the study people (N=60)

Age	n	%
<20	32	53.33
21-29	15	25.00
30-39	7	11.67
≥40	6	10.00
Mean±SD	30±10.42	

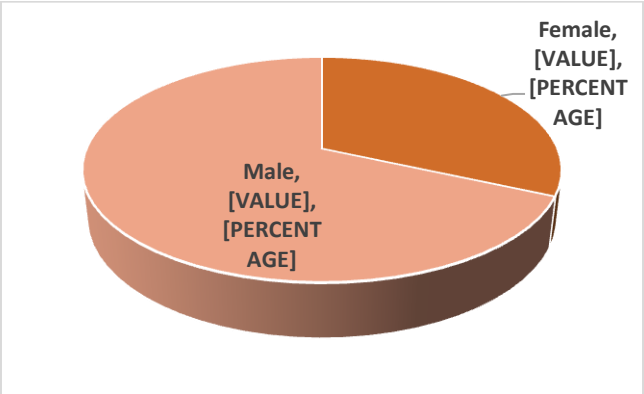

Figure-1: The Gender Distribution of the Study People(N=60)

Table-2: Distribute the study people according to the following symptoms (N=60)

Symptoms	n	%
Fever	60	100.00
Progressive pallor	58	96.67
History of blood transfusion	21	35.00
Bleeding manifestation	17	28.33
Palpitation	2	3.33
Convulsion	1	1.67

Table-3: The clinical findings of the study patients (N=60%)

Clinical findings	**n**	%
Bony tenderness	35	58.33
Splenomegaly	29	48.33
Lymphadenopathy	28	46.67
Oral ulcer	28	46.67
Hepatomegaly	22	36.67
Distended abdomen	6	10.00
Oliguria	5	8.33
Leg oedema	5	8.33
Ascitis	3	5.00
Basal Crepitation	3	5.00

Jaundice	2	3.33
Haematuria	1	1.67
Facial Oedema	1	1.67

Table-4: Biological feature of the study patients(N=100)

Parameters	**Range (minimum-maximum)**	**Mean±SD**
Total WBC count (x109/L)	6-435	52.51±78.70
Hb% (gm/dl)	4.1-13.4	9.25±1.49
Platelet (x109/L)	5-20000	505.20±2815.29
Blast in PBF (%)	Oct-90	53.80±21.251
S. LDH (U/L)	198-11863	1591.53±2195.47
S. uric acid (mg/dL)	1.40-30.03	5.76±4.61
S. inorganic phosphate (mg/dL)	2.30-7.70	4.19±1.20
S. potassium (mmol/L)	2.50-5.40	3.92±0.56
S. calcium (mg/dL)	1.10-11.80	8.33±2.08
S. creatinine (mg/dL)	0.19-3.59	89±0.55

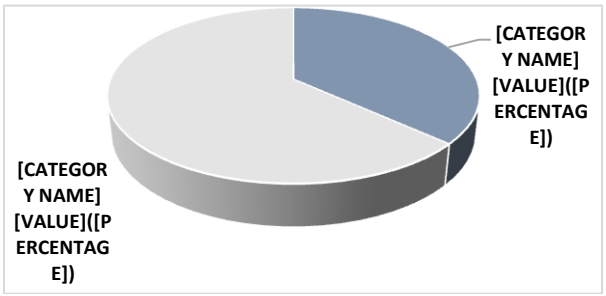

Figure-2: Immunophenotyping of ALL Patients:

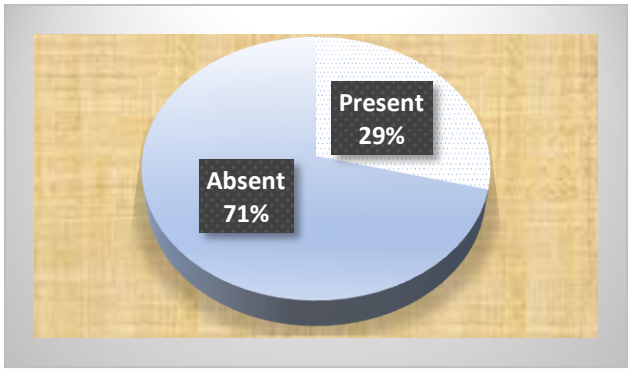

Figure-3: Prevalence of TLS among ALL patients (n=60)

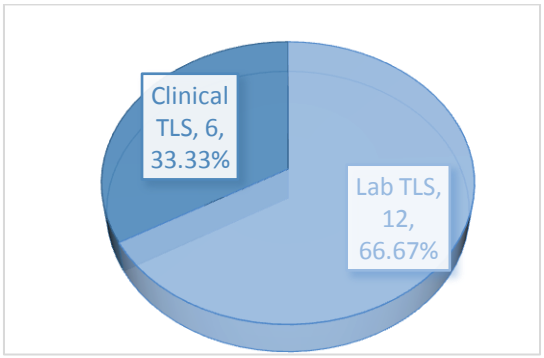

Figure 4: Distribution of lab and clinical TLS among TLS patients (n=18)

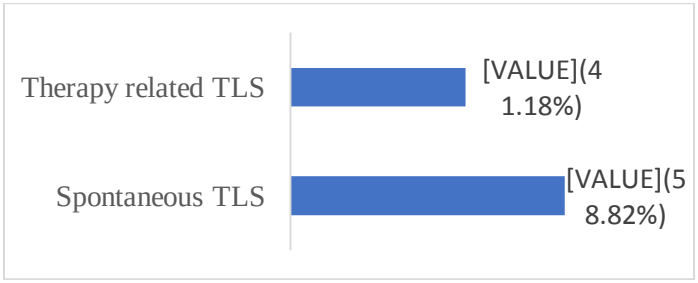

Figure-5: Distribution of TLS According to Onset

V. Discussion

The pathogenesis of ALL involves the abnormal proliferation and differentiation of a clonal population of lymphoid cells. In this study the age distribution of the study people about 32(53.33%) respondents were less than 20 years old and followed by 15(25.00%) from 21-29 years, 7(11.67%) from 30-39 years, 6(10.00%) from ≥40 years. The Mean age was 30±10.42. In a study conducted by Saleem et al found the mean age 47 which is more than our study[18]. Memon et al. studied 91 children aged 2-13 years and mean age of 6.39±3.08 years[19]. There followed in the gender distribution of the study people where male was 41(68.33%) and female was 19(31.67%). Males were found predominant than female in this study. Most of the clinical manifestations of ALL reflect the accumulation of malignant, poorly differentiated lymphoid cells within the bone marrow, peripheral blood, extramedullary sites. There found the following symptoms where Fever was found in 60(100.00%) cases and followed by Progressive pallor in 58(96.67%), History of blood transfusion in 21(35.00%), Bleeding manifestation in 17(28.33%), Palpitation in 2(3.33%) and Convulsion in 1(1.67%). Presentation can be nonspecific, with a combination of constitutional symptoms and signs of bone marrow failure (anemia, thrombocytopenia, leukopenia). Common symptoms include 'B symptoms' (fever, weight loss, night sweats), easy bleeding or bruising, fatigue, dyspnea and infection. Involvement of extramedullary sites commonly occurs and can cause lymphadenopathy, splenomegaly or hepatomegaly in 20% of patients.[20] CNS involvement at time of diagnosis occurs in 5–8% of patients and present most commonly as cranial nerve deficits or meningismus.[21] We found in the clinical findings of the study patients' Bony tenderness was found in 35(58.33%) and followed by Splenomegaly in 29(48.33%), Lymphadenopathy in 28(46.67%), Oral ulcer in 28(46.67%), Hepatomegaly in 22(36.67%), Distended abdomen in 6(10.00%), Oliguria in 5(8.33%), Leg oedema in 5(8.33%), Ascitis in 3(5.00%), Basal Crepitation in 3(5.00%), Jaundice in 2(3.33%), Haematuria in 1(1.67%) and Facial Oedema in 1(1.67%). A study conducted in Children on the 79 patients, arrhythmia was observed in 6 cases (7.5%), epilepsy in 3 cases (3.8%), high creatinine in 33 cases (41.7%), and oliguresis in 8 cases (10.1%). As to the distribution of abnormal laboratory indexes, hyperphosphatemia occurred with the highest frequency (68.8%) and hyperkalemia occurred with the lowest frequency (35.4%).[22] Diagnosis is established by the presence of 20% or more lymphoblasts in the bone marrow or peripheral blood.[20] Cairo-Bishop has developed specific laboratory criteria and guidelines to define TLS in terms of its severity based on the degree of serum creatinine elevation, the presence of and type of cardiac arrhythmia, and the presence and severity of seizures.[23] If there are two or more of any of a specific criterion of abnormalities in the body, one can be diagnosed with laboratory TLS. This includes a serum uric acid level ≥8 mg/dL, or a 25% increase from baseline; a serum potassium level ≥ 6 mmol/L, or a 25% increase from baseline; serum phosphate levels ≥ 6.5 mg/dL in children and ≥4.5 mg/dL in adults, or a 25% increase from baseline; and a serum calcium level ≤7 mg/dL, or a 25% decrease from baseline.[24] The biological feature of the study patients. Menon et al found in his study with ALL on risk categories, immunophenotyping, laboratory parameters like complete blood picture, serum creatinine (SCr), potassium (K), calcium (Ca), phosphorus (P) and uric acid (UA) on day 0,3 and 7 after chemotherapy. In our study the range of Total WBC count (x109/L) was (6-435) and the Mean±SD was 52.51±78.70 and followed by Hb% (gm/dl) was (4.1-13.4) and 9.25±1.49, Platelet (x109/L) was (5-20000) and 505.20±2815.29. Blast in PBF (%) was (Oct-90) and 53.80±21.251. S. LDH (U/L) was (198-11863) and 1591.53±2195.47. S. uric acid (mg/dL) was (1.40-30.03) and 5.76±4.61. S. inorganic phosphate (mg/dL) was (2.30-7.70) and 4.19±1.20. S. potassium (mmol/L) (2.50-5.40) and 3.92±0.56. S. calcium (mg/dL) was (1.10-11.80) and 8.33±2.08. S. creatinine (mg/dL) was (0.19-3.59) and 89±0.55. The immunophenotyping of ALL patients where B Cell was in 38(63.33%) and T Cell was in 22(36.67%) cases. From the prevalence of TLS among all patients and among them 71% were absent and 29% were present. The lab and clinical frequency of TLS among TLS patients where clinical TLS was in 6(33.33%) and Lab TLS was in 12(66.67%). In the distribution of TLS according to onset where therapy related TLS was in 7(41.18%) and spontaneous TLS was in 11(58.82%) cases. A study conducted in China on childhood tumor lysis syndrome he found that the laboratory findings high WBC count.[25]

Limitations of The Study

This study has some limitations as well. As this study is conducted in only one hospital, hence there was no scope for the comparison with others hospitals' condition. Besides, there were only 60 respondents in this study which is another limitation. Besides, the lack of budget, limited study period, unavailability of proper data, unwillingness of all the patients to response were the major limitation of this study.

VI. Conclusion & Recommendation

TLS is a hypothetically preventable but a life-threatening problem. Rasburicase is thought to probably reduce the incidence and severity of TLS. The incidence of TLS is increasing because of more effective cancer treatments in recent years and hence it is required to pay due attention in this matter. Standard and universally accepted diagnostic criteria for TLS need to follow to start therapy instantly, to precise all restrictions before cancer treatment, to assess incidence and pathogenesis, and to select treatment options. For successful management and treatment of TLS it is recommended that prompt identification of clinical and laboratory characteristics, signs and symptoms of patients with TLS should be the primary concern. During treatment, patients should be closely monitored by simple biochemical tests. In TLS appropriate incidence and pathogenesis assessment and management can make difference between life and death.

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