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Original Article

Incidence, Risk Factors, and Outcome of Tumor Lysis Syndrome in Hospitalized Children (1–12 Years) with Malignancy

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Abstract

Introduction Oncological emergencies such as tumor lysis syndrome (TLS) can strike before or during the start of chemotherapy. TLS is an important cause of death in children with malignancies. Understanding the risk factors and timely management can prevent mortality in these children.

Objectives We performed this study to determine the incidence and risk factors for TLS in hospitalized children (1–12 years old) with malignancy and assess the outcomes in terms of the need for renal replacement therapy, residual kidney dysfunction, and death.

Materials and Methods A prospective observational cohort study was performed for 18 months, and newly diagnosed children with malignancy aged 1 to 12 years with TLS were enrolled. They were followed to assess risk factors for TLS and their outcome.

Results TLS was strongly correlated to the white blood cell count and spleen size at presentation. Uric acid was the most common parameter affected. Most patients developed TLS on day 1 of chemotherapy initiation.

Conclusion Total leucocyte count ($\geq$50,000 mm^3) and spleen size more than 3 cm below the costal margin are associated with a higher risk of developing TLS and can be closely followed up for the development of TLS. The use of rasburicase lowers the incidence of TLS and the complications associated with raised uric acid levels.

Keywords
- tumor lysis syndrome
- oncological
- emergency
- leukemia
- malignancy

Introduction

The rapid breakdown of the tumor cells leads to leakage of intracellular substances into the blood, which constitutes an oncological emergency known as tumor lysis syndrome (TLS). Clinically, TLS is marked by elevated levels of phosphate (hyperphosphatemia), low calcium levels (hypocalcemia), high uric acid (hyperuricemia), and elevated potassium (hyperkalemia), which can cause secondary hypocalcemia, kidney failure, seizures, and cardiac arrhythmias. Early detection and management are critical.[1] Spontaneous TLS is uncommon but can result in severe clinical consequences.[2]

The exact frequency of TLS is not well established as it varies across different types of cancer. It is most commonly observed in hematological malignancies that are bulky, aggressive, and have a high cellular turnover rate, as well as in tumors that are highly responsive to treatment, such as acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL), particularly Burkitt's lymphoma, multiple myeloma, and other high-proliferative solid tumors.[3]

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Additionally, TLS is frequently observed in solid tumors such as hepatoblastoma and grade 4 neuroblastoma.[4]

Several risk factors contribute to the development of TLS, including splenomegaly ($\geq$ 3 cm below the costal margin [BCM]), hepatomegaly, children with T-cell ALL, children with lactate dehydrogenase (LDH) levels $\geq$ 500 U/L, an initial total leukocyte count (TLC) $\geq$ 20,000 mm^3, poor urine output, use of nephrotoxic drugs, clinical dehydration, and involvement of the central nervous system or kidneys.[5] Recognizing these risk factors can aid in the early identification of children at risk, enabling timely intervention to diagnose and prevent TLS complications.

While most TLS cases respond to medical treatment, complications can still occur, including acute kidney injury (AKI), residual renal dysfunction requiring dialysis, sepsis, acute respiratory failure, gastrointestinal hemorrhage, cerebral hemorrhage, cardiopulmonary arrest, seizures, and even death. A study of 187 patients with TLS with acute myeloid leukemia (AML)[6] reported a 36% incidence of AKI, with 8% of patients requiring dialysis. This was significantly higher compared with other complications such as acute renal failure (58%), the need for dialysis (15%), sepsis (21%), acute respiratory failure (23%), gastrointestinal hemorrhage (6%), cerebral hemorrhage (2%), cardiopulmonary arrest (2%), seizures (1%), and a mortality rate of 21% among 28,370 admitted patients with TLS across various malignancies such as NHL (30%), solid tumors (20%), AML (19%), and ALL (13%).[7]

In conclusion, TLS is a significant factor contributing to early mortality in childhood cancers. However, there are limited data on optimal treatment and risk management from resource-limited settings in low- to middle-income countries (LMICs). As pediatric cancer outcomes improve, there is a need for more data from LMICs to identify risk factors and outcomes for early detection and appropriate management of TLS. This study was conducted to determine the incidence and risk factors for TLS in hospitalized children (ages 1–12 years) with cancer and to assess outcomes related to the need for renal replacement therapy, residual kidney dysfunction, and mortality.

Materials and Methods

Study Design

A prospective observational cohort study was conducted at a tertiary care hospital.

Study Period

The study was conducted over 18 months from July 2020 to December 2021.

Sample Size

The sample size consists of 115 newly diagnosed children aged 1 to 12 years with malignancy (70 males and 45 females).

Inclusion Criteria

The study enrolled 115 newly diagnosed children, aged 1 to 12 years, who were admitted for induction chemotherapy. Participation was contingent on obtaining informed written consent from their parents or guardians.

Exclusion Criteria

Children who were already undergoing chemotherapy, those with refractory or relapsed cancer, and those who refused chemotherapy were excluded from the study.

The malignancies were classified as high risk and low risk based on their propensity to develop TLS. High-risk malignancies included ALL, AML, and Burkitt's lymphoma, whereas low-risk malignancies included solid tumors and indolent lymphomas such as Hodgkin's lymphoma.

Data were collected using a predesigned form to capture details such as demographic information, clinical presentation, underlying disease, relevant medical history, and physical examination findings. TLS was diagnosed according to the Cairo–Bishop criteria.

According to the Cairo–Bishop criteria,[8] laboratory TLS (L-TLS) is diagnosed when at least two of the following conditions are met within a time frame of 3 days before to 7 days after the initiation of chemotherapy:

1. Uric acid levels of more than 4.76 mmol/L (8 mg/dL) or 25% higher than the reference range.
2. Potassium levels of more than 6.0 mmol/L (6 mEq/L) or 25% higher than the reference range.
3. Phosphate levels of more than 2.1 mmol/L (for children, 6.5 mg/dL) or 1.45 mmol/L (for adults) or 25% higher than the reference range.
4. Calcium levels less than 1.75 mmol/L (8 mg/dL) or 25% lower than the reference range.

Cairo–Bishop defined clinical TLS (C-TLS) as L-TLS with any of the following conditions: cardiac arrhythmias, seizures, sudden death, or creatinine 1.5 times the upper limit of normal (adjusted for age).

Upon admission, baseline laboratory biochemical parameters—including serum creatinine, potassium, phosphate, uric acid, calcium, LDH, blood urea nitrogen, and an electrocardiogram (ECG) for cases where potassium exceeded 5.5 mEq/L—were recorded. Baseline hematological parameters such as hemoglobin, hematocrit, TLC, platelet count, and blast count were also documented.

The patients were monitored for TLS 3 days before to 7 days after initiation of induction as per Cairo–bishop criteria.

As a part of the department treatment policy, all patients were prophylactically started on hyperhydration with fluids at the rate of 3,000 mL/m^2/d along with tablet allopurinol at the dose of 300 mg/m^2/d and strict input output monitoring. Injection rasburicase was given to those patients with laboratory evidence of hyperuricemia (>8 mg/dL).

Children were monitored every 24 hours for signs of laboratory and clinical tumor lysis as outlined by the Cairo–Bishop criteria. On admission, they were assessed for baseline demographic characteristics, clinical presentations, and biochemical parameters. Biochemical monitoring was performed every 24 hours to detect any evidence of TLS. ECGs were conducted whenever hyperkalemia or

hypocalcemia was identified, as detailed in the methodology. Additionally, children were monitored for seizures, arrhythmias, and sudden deaths related to electrolyte imbalances.

Statistical Analysis

Categorical variables were reported as counts and percentages, whereas continuous variables were described using either the mean ± standard deviation or median values. The Kolmogorov–Smirnov test was used to assess data normality, with nonparametric tests applied if normality was rejected.

Statistical Tests

1. To compare the quantitative variables between the TLS and non-TLS groups, the unpaired *t*-test or the Mann–Whitney's test will be employed if the data do not have a normal distribution.
2. The chi-square test or Fisher's exact test will be used to compare the qualitative variables.
3. Univariate and multivariate logistic regression will be used to identify risk factors for TLS.

All data will be deemed statistically significant if the *p*-value is less than 0.05. Data will be entered into an MS Excel spreadsheet and analyzed using the licensed version of the Statistical Package for Social Sciences (SPSS) version 21.0.

Ethical Approval

Ethical approval for the study was obtained from the Institutional Ethical Review Board of Vardhaman Mahavir Medical College and Safdarjung Hospital, New Delhi, India, on December 10, 2020 (approval number: IEC/VMMC/SJH/Thesis/2020-11/CC-235). The study's participants received complete information about the research and were reassured that their decision to participate would not impact their medical care. Written consent was obtained, with one copy placed in the child's hospital record and another provided to the participants. All procedures adhered to the institutional research committee's ethical guidelines, the Declaration of Helsinki of 1964 and its subsequent revisions, and other relevant ethical standards.

Results

The distribution of patients by type of malignancy in the study population ($n = 115$) is presented in ►**Table 1**.

During the study period, 26 out of 115 children met the criteria for laboratory tumor lysis syndrome (L-TLS), resulting in an incidence rate of 22.6% (95% confidence interval: 15.6–31.5%). TLS developed in 25 out of 107 patients (23.3%) in high-risk malignancies, whereas in low-risk malignancies, only one patient out of eight patients (12.5%) developed TLS.

Five patients out of 26 patients of L-TLS progressed to C-TLS, out of which 3 patients had B-cell ALL, 1 patient had AML, and 1 patient had a case of Burkitt's lymphoma. Four patients developed C-TLS on day 1 of induction, whereas one patient developed C-TLS on day 3 of induction. Serum creatinine was the most common biochemical abnormality found in all cases of C-TLS. All C-TLS cases of L-TLS developed AKI on day 1 of induction chemotherapy out of which four patients developed persistent renal dysfunction on day 7 of induction therapy in the form of decreased urine output and deranged serum creatinine level and one patient of C-TLS required hemodialysis. Three patients out of five patients with C-TLS died during induction (60%).

►**Fig. 1** demonstrates the association between TLS and the type of malignancy. TLS developed majorly in hematological malignancies as compared with solid tumors. TLS developed in 16 out of 80 patients of B-cell ALL, 3 out of 8 patients with AML, all 2 patients with Burkitt's lymphoma, 4 out of 17 patients with T-cell ALL, and 1 patient with Hodgkin's lymphoma. TLS occurred maximum on day 1 of initiation of induction chemotherapy in children (10 out of 26, or 38.4%). Of the 26 L-TLS cases, 5 progressed to C-TLS. Among these, three patients had B-cell ALL, one patient had AML, and one patient had Burkitt's leukemia. Serum creatinine was the most common biochemical abnormality observed in all cases of C-TLS, and mortality occurred in 60% of patients with C-TLS.

Hyperuricemia (92%) was the most common biochemical abnormality found in L-TLS, that is, 24 out of the 26 children who developed tumor lysis, followed by hyperphosphatemia (73%), hyperkalemia (46%), and hypocalcemia (13%).

Table 1 Distribution of patients in terms of type of malignancy in the study population ($n = 115$)

Type of malignancy	Frequency	Percentage (%)	95% CI (%)
AML	8	7.0	3.3–13.7
B-ALL	80	69.6	60.2–77.6
Burkitt's lymphoma	2	1.7	0.3–6.8
T-ALL	17	14.8	9.1–22.9
Hodgkin's lymphoma	1	0.9	0.0–5.5
Rhabdomyosarcoma	3	2.6	0.7–8.0
Retinoblastoma	2	1.7	0.3–6.8
Mature teratoma	1	0.9	0.0–5.5
Neuroblastoma	1	0.9	0.0–5.5

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval.

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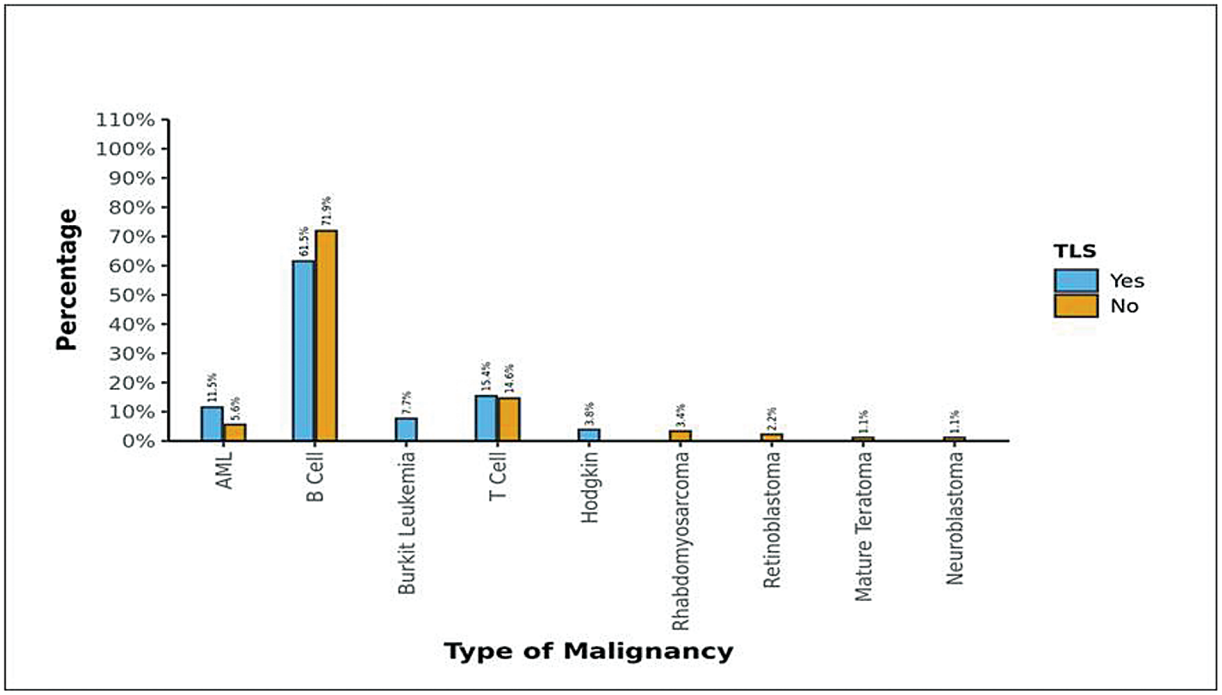

Fig. 1 Association between tumor lysis syndrome (TLS) and the type of malignancy.

Patients were categorized into three groups based on TLC: TLC less than 50,000 mm^3, between 50,000 and 100,000 mm^3, and TLC more than 100,000 mm^3. Children with TLC $\geq$50,000 mm^3 were at a significantly higher risk of developing TLS, with the risk being significant in both univariate and multivariate analyses.

Additionally, patients were categorized into two groups based on spleen size: less than 3 cm or more than 3 cm BCM. With a *p*-value of 0.026, the two groups had a significant difference. Therefore, splenomegaly more than 3 cm BCM is identified as an independent risk factor for the development of TLS, as shown in ►**Table 2**.

Rasburicase was effectively used during the study period in 26 patients with L-TLS, significantly lowering uric acid levels and reducing the incidence of C-TLS and AKI.

No patients with C-TLS developed seizures or cardiac arrhythmias. There were no significant differences between the TLS and non-TLS groups regarding age, gender, or residence in the development of TLS.

Discussion

This prospective study conducted at a tertiary health care center involved 115 children aged 1 to 12 years with newly diagnosed malignancies, aiming to assess the incidence, risk factors, and outcomes of TLS during the induction phase of chemotherapy.

In 1993, Hande and Garrow[7] described TLS as a distinct clinical condition, distinguishing between L-TLS and C-TLS. However, their criteria did not account for patients with preexisting abnormal laboratory findings. Cairo and Bishop later refined the definition of L-TLS to include significant changes in serum values from baseline, occurring within 3 days before to 7 days after the start of chemotherapy. This updated definition was utilized in our study.

In our cohort of 115 children with malignancies, the incidence of L-TLS was 22.6% (26 children), while 4.34% (5 children) experienced C-TLS. Of those with L-TLS, 38% (10 children) had spontaneous TLS, and 62% (16 children) developed TLS during chemotherapy induction. Our findings indicated a predominance of hematological malignancies among those with TLS, particularly ALL (76%) and AML (11%). Truong et al[9] reported a similar incidence of 22.6% for TLS in a study involving 328 children under 18 years with ALL. Although their study included a broader age range, the findings are comparable to ours, which focused on children aged 1 to 12 years. Naeem et al[10] found a higher incidence of TLS (62.6% for L-TLS and 14% for C-TLS) in a study of 91 children

Table 2 Association between TLS and sign: splenomegaly more than 3 cm ($n = 115$)

Splenomegaly more than 3 cm below the coastal margin	TLS			Chi-square test	
	Yes	No	Total	Chi-square test	*p*-Value
Yes	23 (88.5%)	53 (59.6%)	76 (66.1%)	7.504	0.006
No	3 (11.5%)	36 (40.4%)	39 (33.9%)		
Total	26 (100.0%)	89 (100.0%)	115 (100.0%)		

Abbreviation: TLS, tumor lysis syndrome.

with ALL, with 28% experiencing spontaneous TLS and 72% developing TLS as a result of chemotherapy.

In our study, hyperuricemia was the most common biochemical abnormality among those with L-TLS (92%), followed by hyperphosphatemia (73%), hyperkalemia (46%), and hypocalcemia (13%). For C-TLS cases, hyperuricemia and hyperphosphatemia were present in 80 and 60% of cases, respectively. All C-TLS cases developed AKI, with 80% of these patients showing residual renal dysfunction, including reduced urine output and elevated serum creatinine levels on day 7 of chemotherapy, and one patient required hemodialysis.

The lower incidence of TLS in our study compared with others can be attributed to preventive measures such as hyperhydration therapy and the use of uric acid-lowering medications such as allopurinol and rasburicase. During the study period, rasburicase was administered to 26 patients with L-TLS, effectively reducing uric acid levels and the occurrence of C-TLS and AKI. The ability to anticipate and prevent the development of TLS is the most crucial factor taken into account when managing the condition. Maintaining adequate urine production and reducing blood levels of phosphate, potassium, and uric acid are the primary objectives of prophylaxis. It is advised that biological values be checked every 4 to 6 hours for high-risk patients, every 8 to 12 hours for intermediate-risk patients, and every day for low-risk patients after beginning chemotherapy. To enhance renal perfusion, glomerular filtration, and urine output, aggressive intravenous hydration is essential for preventing TLS in high-risk patients. Aggressive hydration should begin prior to the commencement of treatment for tumors that have a high potential to release a significant amount of intracellular chemicals following the start of chemotherapy. Diuretics may be used to promote urine output in patients with underlying kidney or heart disorders, but careful fluid management and monitoring are crucial to prevent fluid overload.

Our findings align with those of Naeem et al[10] who also noted hyperuricemia and hyperphosphatemia as prevalent abnormalities in both L-TLS and C-TLS cases. Truong et al[9] observed hypocalcemia as the most common laboratory abnormality in 45.1% of patients, with concurrent abnormalities of calcium and phosphate being less frequent. Montesinos et al[11] reported hyperphosphatemia as the most common finding in 61% of TLS cases, with hyperuricemia present in 45% of cases. Renal failure was significantly more common in patients with TLS compared with those without TLS during induction therapy.

Our study identified splenomegaly exceeding 3 cm BCM and a raised TLC ($>50{,}000/mm^3$) as risk factors for TLS. Additionally, a higher proportion of male participants (60%) was noted, reflecting a tendency in India for preferential health-seeking behavior for male children.

Patients were classified into standard-risk and high-risk groups by Naeem et al[10] based on various factors, while Truong et al[9] identified predictors such as male sex, age over 10 years, T-ALL, hepatomegaly, splenomegaly, high LDH levels, and a raised TLC ($>50{,}000/mm^3$) as risks for TLS.

In our study, four children developed TLS before starting induction chemotherapy, representing 17.39% of all TLS cases. Montesinos et al[11] reported that 25% of children with AML showed TLS before induction. Razis et al[12] found a 57% incidence of TLS in children with hyperleukocytic leukemia, while our study found an 81.81% incidence at TLC levels above $50{,}000\ mm^3$.

Different chemotherapy regimens may influence the incidence of TLS in various malignancies.

Strengths and Limitations

This prospective study provides comprehensive follow-up and outcome data up to day 7 of chemotherapy, minimizing bias. However, the study population predominantly consisted of acute leukemia cases, with few instances of other high-risk malignancies such as NHL. The study's setting in a tertiary care center may introduce referral bias. Also, the study was performed at a single center and is therefore limited by a small sample size.

Conclusion

The incidence of L-TLS in Indian children with malignancies is 22.6%, and C-TLS is 4.34%. Higher TLC ($\geq 50{,}000\ mm^3$) and splenomegaly exceeding 3 cm BCM are associated with an increased risk of TLS. Rasburicase use effectively reduces TLS incidence and related complications.

Patient Consent

Informed consent was obtained from each patient.

Authors' Contributions

Each author has contributed equally to the preparation of the manuscript. The concept and design of the manuscript were done by S.S. and A.S., the literature search was done by V.K., N.G., and S.S. Data acquisition was done by V.K. and A.S. Data analysis and statistical analysis were done by V.K., S.S., and A.S. Manuscript preparation and manuscript editing were done by V.K., N.G., R.D., and N.G.

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None.

Conflict of Interest

None declared.

References

1 Tannock I. Cell kinetics and chemotherapy: a critical review. Cancer Treat Rep 1978;62(08):1117–1133
2 Hochberg J, Cairo MS. Tumor lysis syndrome: current perspective. Haematologica 2008;93(01):9–13
3 Mirrakhimov AE, Ali AM, Khan M, Barbaryan A. Tumor lysis syndrome in solid tumors: an up to date review of the literature. Rare Tumors 2014;6(02):5389
4 Sevinir B, Demirkaya M, Baytan B, Güneş AM. Hyperuricemia and tumor lysis syndrome in children with non-Hodgkin's lymphoma and acute lymphoblastic leukemia. Turk J Haematol 2011;28(01):52–59

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5 Lahoti A, Kantarjian H, Salahudeen AK, et al. Predictors and outcome of acute kidney injury in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome. Cancer 2010;116(17):4063–4068
6 Durani U, Shah ND, Go RS. In-hospital outcomes of tumor lysis syndrome: a population-based study using the National Inpatient Sample. Oncologist 2017;22(12):1506–1509
7 Hande KR, Garrow GC. Acute tumor lysis syndrome in patients with high-grade non-Hodgkin's lymphoma. Am J Med 1993;94 (02):133–139
8 Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127(01):3–11
9 Truong TH, Beyene J, Hitzler J, et al. Features at presentation predict children with acute lymphoblastic leukemia at low risk for tumor lysis syndrome. Cancer 2007;110(08):1832–1839
10 Naeem B, Moorani KN, Anjum M, Imam U. Tumor lysis syndrome in pediatric acute lymphoblastic leukemia at tertiary care center. Pak J Med Sci 2019;35(04):899–904
11 Montesinos P, Lorenzo I, Martín G, et al. Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model. Haematologica 2008;93(01):67–74
12 Razis E, Arlin ZA, Ahmed T, et al. Incidence and treatment of tumor lysis syndrome in patients with acute leukemia. Acta Haematol 1994;91(04):171–174

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