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Risk Factors for Tumor Lysis Syndrome in Patients with Acute Lymphocytic Leukemia Treated in a Tertiary Care Hospital

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Abstract **Original Research Article**

Background: Tumor lysis syndrome (TLS) is the combination of metabolic and electrolyte abnormalities (hyperuricemia, hyperkalaemia, hyperphosphatemia, and secondary hypocalcemia) which occurs in patients with cancer spontaneously and usually after the initiation of cytotoxic treatment and it can cause serious clinical complications like acute kidney injury and cardiac arrest. ***Aim of the study*:** The aim of the study was to identify the associated risk factors of tumor lysis syndrome (TLS) in patients with Acute Lymphoblastic Leukemia (ALL) in a tertiary care hospital. ***Methods:*** This cross-sectional study was conducted by Department of Hematology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh October 2019 to September 2020. Newly diagnosed case of Acute Lymphoblastic Leukemia patients admitted in the department of Hematology in BSMMU, Dhaka during the study period. The study was approved by the local ethical committee and all patients gave their informed consent to take part in this investigation. Data were compiled and analyzed using the Statistical Program for Social Science (SPSS-21) version, and organized by using MS-Excel 2016. ***Results:*** TLS was absent in 34 and present in 17 cases. Within 3 days before chemotherapy, Hyperuricemia (>8.0 mg/dl) was found in 12(70.59%) cases and was absent in 1(2.33%) cases. Within 7 days after initiation of induction chemotherapy, Hyperuricemia (>8.0 mg/dl) was seen in 13(76.47%) cases. 12(70.59%) respondents were <20 years who were with TLS and 23(53.49%) case were not with TLS and followed by 7(41.18%) cases with TLS were from ≥20 years and 20(46.51%) were not with TLS. B cell type with TLS was found in 7(41.18%) and without TLS was 33 (76.74%) cases and followed by T cell type in 10(58.82%) cases and 10(23.26%) case. Initial WBC count (>50.0 x109/L) OR was 2.12 where 95% CI was lower in 0.91 and upper in 7.16. S. LDH (≥1000 U/L) OR was 13.07 and 95% CI was lower in 1.93 and upper in 101.23. ***Conclusion:*** In this study, it was observed that tumor lysis syndrome (TLS) was common in patients with Acute Lymphocytic Leucaemia (ALL), where in spontaneous onset and lab TLS was more frequent than therapy induced TLS and clinical TLS.

Keywords: Tumor Lysis Syndrome, Acute Lympholastic Leukemia, Risk Factor.

INTRODUCTION

Tumor lysis syndrome (TLS) is the combination of metabolic and electrolyte abnormalities (hyperuricemia, hyperkalaemia, hyperphosphatemia, and secondary hypocalcemia) which occurs in patients with cancer spontaneously and usually after the initiation of cytotoxic treatment and it can cause serious clinical complications like acute kidney injury and cardiac arrest. TLS is the most common disease in hematologic cancers [1]. It is mostly associated with hematological malignancies such as AML, ALL, NHL especially, Burkitt lymphoma, which needs prompt recognition through aggressive management [2, 3]. TLS

has also been more common in cancers that are associated with metastatic colon cancer such as endometrial cancer, hepatocellular carcinoma, CLL, and chronic myelogenous leukemia [4-7]. Patients often show chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine [8]. Identification of tumor- and patient-specific risk factors for TLS and early recognition of laboratory and clinical TLS based on established criteria are essential for preventing TLS [9]. The risk is based on several factors, including age, type and stage of cancer, lactate dehydrogenase (LDH) level, white blood cell (WBC) count, and patient comorbidity [10]. A high level of solutes, low solubility, slow urine flow, and high levels of co-crystallizing substances favor crystal formation and increase the severity of TLS [11]. 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 [12]. Several authors had encouraged guidelines for risk stratification and made recommendations for evaluating risk and for prophylactic therapy for the tumor lysis syndrome and rasburicase is recommended as first-line treatment for patients with high risk for clinical TLS [13]. Due to cost considerations and pending pharmacoeconomic studies, no consensus has been reached on rasburicase use in patients with intermediate risk for TLS; some have advocated use of a small dose of rasburicase in such patients [14, 15]. Patients with low risk can usually be treated with intravenous fluids with or without allopurinol, but they should be monitored daily for signs of the TLS. If untreated, TLS can lead to complications such as acute renal failure, cardiac arrhythmias, seizures, multiple organ failure and sudden death [16]. However, TLS is treatable if properly managed. Early detection of TLS is crucial for appropriate prophylaxis and treatment as it is one of the most common life-threatening oncological emergencies encountered [17].

OBJECTIVE

This cross-sectional study was conducted to identify associated risk factors of tumor lysis syndrome in patients with Acute Lymphoblastic Leukemia in a tertiary care hospital.

MATERIALS AND METHODS

This cross-sectional study was conducted by Department of Hematology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh October 2019 to September 2020. Newly diagnosed case of Acute Lymphoblastic Leukemia patients admitted in the department of Hematology in BSMMU, Dhaka during the study period. This study sampling method was consecutive sampling. Clinical history was taken & physical examination was evaluated; baseline electrocardiography of each patient was recorded at presentation. Venous blood samples were drawn in EDTA tube for total leucocyte count (TLC). 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. 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. Inclusion criteria were all newly diagnosed Acute Lymphoblastic Leukemia patients on the basis of CBC with PBF, bone marrow study and immunophenotyping. Exclusion criteria were relapsed and secondary case of Acute Lymphoblastic Leukemia, known case of epilepsy and other convulsive disorder and known case of chronic kidney disease. The study was approved by the local ethical committee and all patients gave their informed consent to take part in this investigation. Data were compiled and analyzed using the Statistical Program for Social Science (SPSS-21) version, and organized by using MS-Excel 2016.

RESULT

This cross-sectional study was aimed to identify the associated risk factors of tumor lysis syndrome (TLS) in patients with Acute Lymphoblastic Leukemia (ALL) in a tertiary care hospital. On this purpose Figure-1 shows the prevalence of TLS among all patients and among them in 34(71.67%) were absent and in 17(28.33%) were present. Figure-2 shows the distribution of lab and clinical TLS among TLS patients where clinical TLS was 6(35.29%) and Lab TLS was 11(64.71%). Figure-3 shows the distribution of TLS according to onset where therapy related TLS was 7(41.18%) and spontaneous TLS was 10(58.82%). Table-1 shows the prevalence of biochemical abnormalities in patients with all with or without TLS. TLS was absent in 34 and present in 17 cases. Within 3 days before chemotherapy, Hyperuricemia (>8.0 mg/dl) was found in 12(70.59%) cases and was absent in 1(2.33%) cases and followed by Hyperkalaemia (>4.5 mg/dl) was in 10(58.82%) cases and was absent in 12(27.91%) cases, Hyperkalaemia (≥6.0 mmol/L)was in 1(5.88%) cases, High s. creatinine (>1.8 mg/dl) was found in 4(23.53%) cases, Hypocalcaemia (<7.0 mg/dl) wasn't found in any cases. Within 7 days after initiation of induction chemotherapy, Hyperuricemia (>8.0 mg/dl) was seen in 13(76.47%) cases, Hyperkalaemia (>4.5 mg/dl) was present in 12(70.59%) cases and was absent in 8(18.60%) cases, Hyperkalaemia (≥6.0 mmol/L) was seen in 8(47.06%) cases, High s. creatinine (>1.4 mg/dl) was in 3.(17.65%) cases, Hypocalcaemia (<7.0 mg/dl)was in 3(17.65%) cases. Table-2 shows the association of different factors with tumor lysis syndrome. TLS was absent in 43 and present in 17. 12(70.59%) respondents were <20 years who were with TLS and 23(53.49%) case were not with TLS and followed by 7(41.18%)

cases with TLS were from ≥20 years and 20(46.51%) were not with TLS. Male participants with TLS were 7(41.18%) cases and without TLS was 26(60.47%). Female with TLS was 5(29.41%) and without TLS was 17(39.53%). In assessing Immunophenotyping B cell type with TLS was found in 7(41.18%) and without TLS was 33 (76.74%) cases and followed by T cell type in 10(58.82%) cases and 10(23.26%) case. Organomegaly with TLS was mostly found in lymphadenopathy, 16(94.12%) cases and without TLS in 13(30.23%) case and followed by Hepato-Splenomegaly in12(70.59%) and 9(20.93%) case. Initial WBC count (x109/L) with TLS was <50 in 7(41.18%) cases and was no TLS was in 36(83.72%) case and followed by ≥50 was in 10(58.82%) and 7(16.28%) case. S. LDH level (U/L) <1000 in TLS was found in 2(11.76%) cases and in no TLS 34(79.07%) case and ≥1000 was in 15(88.24%) and 9(20.93%) case. Table 3 shows multivariate logistic regression to detect independent predictors of developing TLS among ALL patients. The OR was 2.44 in ≥20 years where 95% CI was lower in 0.28 and upper in 21.4 and followed by OR of male was 1.02 where 95% CI was lower in 0.82 and upper in 13.54. Lymphadenopathy OR was 6.95 and 95% CI was lower in 0.45 and upper in 1107.28. Hepato-splenomegaly OR was 3.17 where 95% CI was lower in 0.29 and upper in 34.75. T cell type OR was 3.95 and 95% CI was lower in 0.42 and upper in 36.81. Initial WBC count (>50.0 x109/L) OR was 2.12 where 95% CI was lower in 0.91 and upper in 7.16. S. LDH (≥1000 U/L) OR was 13.07 and 95% CI was lower in 1.93 and upper in 101.23.

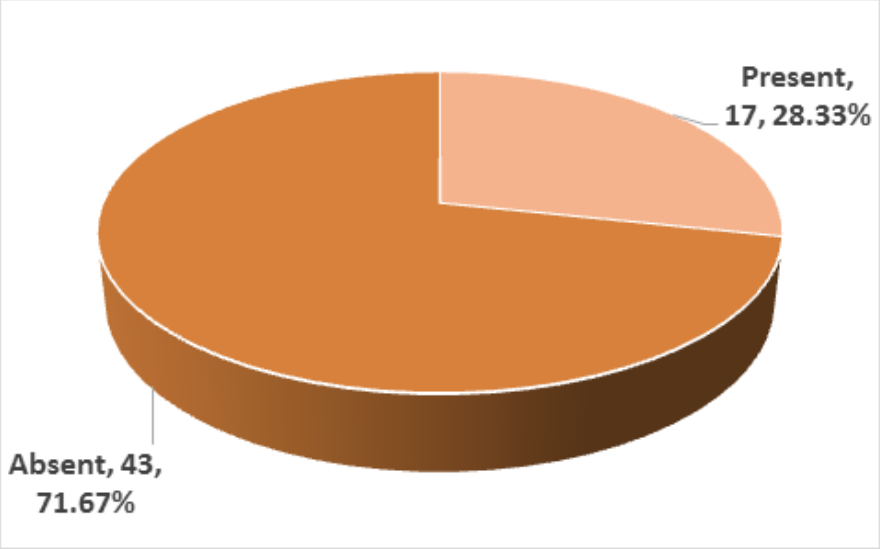

Fig-1: Prevalence of TLS among ALL patients (N=60)

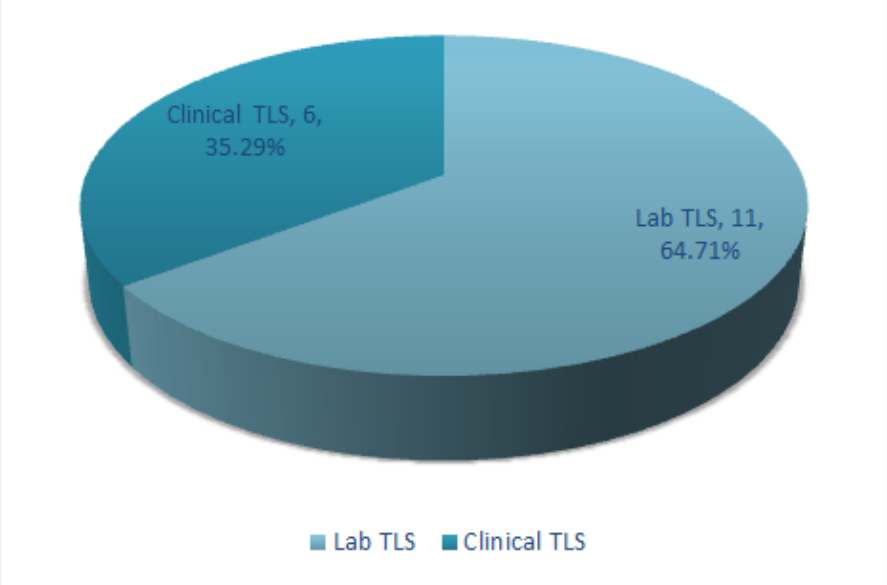

Fig-2: Distribution of lab and clinical TLS among TLS patients (N=17)

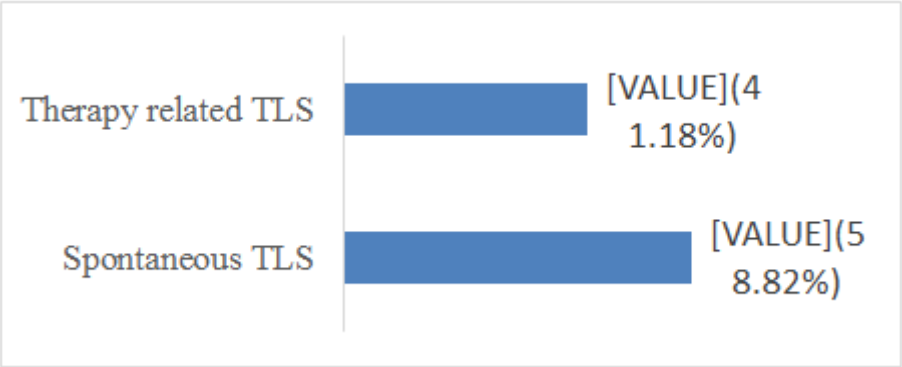

Fig-3: Distribution of TLS according to onset (N=17)

Table-1: Prevalence of biochemical abnormalities in patients with ALL with or without TLS (N=50)

Variables	Tumor lysis syndrome				P value
	Yes		No		
	n=17	%	n=43	%	
Within 3 days before chemotherapy					
Hyperuricemia (>8.0 mg/dl)	12	70.59	1	2.33	<0.001
Hyperkalaemia (>4.5 mg/dl)	10	58.82	12	27.91	0.043
Hyperkalaemia (≥6.0 mmol/L)	1	5.88	0	0.00	0.26
High s. creatinine (>1.8 mg/dl)	4	23.53	0	0.00	0.015
Hypocalcaemia (<7.0 mg/dl)	0	0.00	0	0.00	-
Within 7 days after initiation of induction chemotherapy					
Hyperuricemia (>8.0 mg/dl)	13	76.47	0	0.00	<0.001
Hyperkalaemia (>4.5 mg/dl)	12	70.59	8	18.60	0.002
Hyperkalaemia (≥6.0 mmol/L)	8	47.06	0	0.00	<0.001
High s. creatinine (>1.4 mg/dl)	3	17.65	0	0.00	0.064
Hypocalcaemia (<7.0 mg/dl)	3	17.65	0	0.00	0.064

Table-2: Association of different factors with tumor lysis syndrome (N=60)

Variables	Tumor lysis syndrome				p value
	Yes		No		
	n=17	%	n=43	%	
Age (in years)					
<20	12	70.59	23	53.49	1
≥20	7	41.18	20	46.51	
Gender					
Male	11	64.71	26	60.47	0.742
Female	5	29.41	17	39.53	
Immunophenotyping					
B cell type	7	41.18	33	76.74	0.021
T cell type	10	58.82	10	23.26	
Organomegaly					
Lymphadenopathy	16	94.12	13	30.23	<0.001
Hepato-Splenomegaly	12	70.59	9	20.93	0.005
Initial WBC count (x109/L)					
<50	7	41.18	36	83.72	0.004
≥50	10	58.82	7	16.28	
S. LDH level (U/L)					
<1000	2	11.76	34	79.07	<0.001
≥1000	15	88.24	9	20.93	

Table 3: Multivariate logistic regression to detect independent predictors of developing TLS among ALL patients (N=60)

Predictor	OR	95% CI		p value
		Lower	Upper	
Age ≥20 years	2.44	0.28	21.4	0.421
Male	1.02	0.82	13.54	0.848
lymphadenopathy	6.95	0.45	107.28	0.165
Hepato-splenomegaly	3.17	0.29	34.75	0.344
T cell type	3.95	0.42	36.81	0.228
Initial WBC count (>50.0 x109/L)	2.12	0.91	7.16	0.714
S. LDH (≥1000 U/L)	13.07	1.93	101.23	0.015

DISCUSSION

Tumour lysis syndrome (TLS) is a life-threatening oncological emergency characterized by metabolic abnormalities including hyperuricaemia, hyperphosphataemia, hyperkalaemia and hypocalcaemia [18]. It is essential to identify patients at risk of tumour lysis syndrome (TLS) because this life-threatening condition may occur rapidly and is preventable. However, the purpose of this study was to determine the risk factors for TLS in patients with ALL. After meticulous history taking, examination, and appropriate investigations, a total of 60 patients with ALL were included in this study, all of them met the inclusion and exclusion criteria (relapsed and secondary cases of ALL, known cases of CKD, epilepsy, and other convulsive disorders). The prevalence of TLS among all patients and among them 34(71.67%) were absent and 17(28.33%) were present. TLS prevalence in ALL patients has been observed to range from 25.5 to 39% over the world [19, 20].

The distribution of lab and clinical TLS among TLS patients where clinical TLS was 6(35.29%) and Lab TLS was 11(64.71%). The TLS according to onset where therapy related TLS was 7(41.18%) and spontaneous TLS was 10(58.82%). In 116 patients, the incidence of TLS was 46% (95% CI: 36–55%), with 14 of 53 patients (26%) with TLS requiring dialysis for management of hyperkalaemia or hyperphosphatemia not responsive to medical therapy [21].

In the prevalence of biochemical abnormalities in patients with all with or without TLS, TLS was absent in 34 and present in 17 cases. Within 3 days before chemotherapy, Hyperuricemia (>8.0 mg/dl) was found in 12(70.59%) cases and was absent in 1(2.33%) case and followed by Hyperkalaemia (>4.5 mg/dl) was in 10(58.82%) cases and was absent in 12(27.91%) cases, Hyperkalaemia (≥6.0 mmol/L) was in 1(5.88%) case, High s. creatinine (>1.8 mg/dl) was found in 4(23.53%) cases, Hypocalcaemia (<7.0 mg/dl) wasn't found in any cases. Within 7 days after initiation of induction chemotherapy, Hyperuricemia (>8.0 mg/dl) was seen in 13(76.47%) cases, Hyperkalaemia (>4.5 mg/dl) was present in 12(70.59%) cases and was absent in 8(18.60%) cases, Hyperkalaemia (≥6.0 mmol/L) was seen in 8(47.06%) cases, High s. creatinine (>1.4 mg/dl) was in 3(17.65%) cases, Hypocalcaemia (<7.0 mg/dl)was in 3(17.65%) cases. In the largest analysis of TLS in patients with chronic lymphocytic luekemia (CLL) or (ALL), TLS occurred in 20 (0.33%) of 6,137 patients receiving single agent fludarabine, within 7 days (range 5–14 days) after administration [16].

The association of different factors with tumor lysis syndrome. TLS was absent in 43 and present in 17. 12(70.59%) respondents were <20 years who were with TLS and 23(53.49%) case were not with TLS and followed by 7(41.18%) cases with TLS were from ≥20 years and 20(46.51%) were not with TLS. Male participants with TLS were 7(41.18%) cases and without TLS were 26(60.47%). Female with TLS was 5(29.41%) and without TLS was 17(39.53%) and followed insignificant relationship (P=0.742). But in the study of KA Bulm *et al*. found that patient characteristics highly associated with the occurrence of TLS were female gender (P<0.001) [21].

In assessing Immunophenotyping B cell type with TLS was found in 7(41.18%) and without TLS was 33 (76.74%) cases and followed by T cell type in 10(58.82%) cases and 10(23.26%) case. Organomegaly with TLS was mostly found in lymphadenopathy, 16(94.12%) cases and without TLS in 13(30.23%) case and followed by Hepato-Splenomegaly in12 (70.59%) and 9(20.93%) case. Initial WBC count (x109/L) with TLS was <50 in 7(41.18%) cases and was no TLS was in 36(83.72%) case and followed by ≥50 was in 10(58.82%) and 7(16.28%) case. S. LDH level (U/L) <1000 in TLS was found in 2(11.76%) cases and in no TLS 34(79.07%) case and ≥1000 was in 15(88.24%) and 9(20.93%) case. Truong *et al*. found a strong association between T cell immunophenotype and development of TLS (OR 8.2, 95% CI 4-17, P value <.0001). Similar results found in the study where the occurrence of TLS was associated with significant morbidity with 40% of patients with TLS dying during the first cycle of fludarabine [16].

The OR was 2.44 in ≥20 years where 95% CI was lower in 0.28 and upper in 21.4 and followed by OR of male was 1.02 where 95% CI was lower in 0.82 and upper in 13.54. Lymphadenopathy OR was 6.95 and 95% CI was lower in 0.45 and upper in 1107.28.

Hepato-splenomegaly OR was 3.17 where 95% CI was lower in 0.29 and upper in 34.75. T cell type OR was 3.95 and 95% CI was lower in 0.42 and upper in 36.81. Initial WBC count (>50.0 x109/L) OR was 2.12 where 95% CI was lower in 0.91 and upper in 7.16. S. LDH (≥1000 U/L) OR was 13.07 and 95% CI was lower in 1.93 and upper in 101.23.

Limitations of the study

This single center study with small sample size and both new/old cases were considered which might affect the overall incidence pattern.

CONCLUSION

TLS is actually a preventable disease but the life-threatening complication makes the life difficult of patients. As it is a life-threatening condition, it is essential to identify patients at risk of TLS. Successful management and treatment of TLS is highly dependent on the exact identification of clinical and laboratory characteristics, risks, signs and symptoms of patients. Vigilant assessment and monitoring to recognize TLS and ensure timely response in time of emergency, had been recognized by many experts Although, experts have issued management guidelines for TLS but standardized procedures for assessing risk have been lacking until now. Further guidance is needed for simple risk-prediction models that have a standardized definition of TLS and uniform supportive care guidelines for each cancer type.

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