Clinical and laboratory approach for the identification of the risk for tumour lysis syndrome in children with acute lymphoblastic leukemia.

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Abstract: Tumour lysis syndrome (TLS) is a life-threatening oncological emergency characterized by metabolic abnormalities including hyperuricaemia, hyperphosphataemia, hyperkalaemia and hypocalcaemia. These metabolic complications predispose the cancer patient to clinical toxicities including renal insufficiency, cardiac arrhythmias, seizures, neurological complications and potentially sudden death. TLS is a well-recognized complication of acute lymphoblastic leukemia (ALL). The ability to predict children at differing risk of TLS would be an early step toward risk-based approaches. However with the increased availability of newer therapeutic targeted agents, there are no published guidelines on the risk classification of TLS for individual patients at risk of developing this syndrome. Risk factors included biological evidence of laboratory TLS, proliferation, bulk and stage of malignant tumour and renal impairment at the time of TLS diagnosis. The objectives of the current study were to describe a sensitive prediction rule to identify patients at risk of TLS in childhood ALL. Sixty children aged ≤18 years who were diagnosed as ALL were studied. TLS was defined by the presence of ≥2 laboratory abnormalities occurring in the time of interest (before and 5 days after intiation of chemotherapy). From the total 60 patients include, 45% met criteria for TLS. TLS predictive factors were male sex (odds ratio [OR], 3.0; $P = 0.08$), age ≥10 years (OR, 1.3; $P < 0.2$), splenomegaly (OR, 4.2; $P = 0.008$), generalized lymphadenopathy (OR, 1.0; $P = 0.2$), white blood count (WBC) ≥20 × 10^9/L ($P = < .0001$), T-cell phenotype (OR, 8.0; $P = 0.002$), and lactate dehydrogenase ≥1000 U/L (OR, 5.0; P .002). **In conclusion,** children with ALL who are at low risk for TLS can be identified early at the time of hospital presentation and may benefit from a risk-stratified approach directed at reduced intensity of laboratory monitoring and limited TLS prophylactic measures.
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1. Introduction

Tumor lysis syndrome (TLS) is a group of metabolic abnormalities consists of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia that result from the rapid release of intracellular metabolites such as nucleic acids, proteins, phosphorus and potassium from lysed malignant cells (**Cairo *et al.*, 2010**). This process can potentially cause hyperuricaemia, hyperkalaemia, hyperphosphataemia, with or without hypocalcaemia and uraemia, arrhythmias, seizures and even death. TLS symptoms can occur before (spontaneously) or within 12–72 hrs after initiation of cytoreductive chemotherapy for malignancies (**Kedar *et al.*, 1995; Akoz *et al.*, 2007).**

TLS is most frequently associated with non-Hodgkin lymphoma (NHL), particularly Burritt's lymphoma/leukaemia, as well as other haematological malignancies, such as acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) (**Hochberg & Cairo, 2008; Konuma *et al.*, 2008**), and require prompt recognition followed by aggressive management (**Chen & Chuang, 2009; Choi *et al.*, 2009**).

TLS may also occur in other tumour types, especially tumours sensitive to cytotoxic treatment, which have a high proliferative rate or have a large tumuor size or burden (**Vaisban** et al.**, 2001; Coiffier** et al.**, 2008**). Other studies have been reported the 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 (**Francescone** et al.**, 2009; Lin** et al.**, 2009**).

It is essential to identify patients at risk of TLS because this life-threatening condition may occur rapidly and is preventable. However, standardized procedures for assessing risk have been lacking until now (**Levine, 2002; Cairo *et al.*, 2010**). Complications resulting from TLS, can compromise the efficacy or further administration of chemotherapy (**Yim *et al.*, 2003; Hsu *et al.*, 2004**) and have an impact on morbidity and mortality. They are also associated with longer and more costly

hospital stays (**Annemans *et al.*, 2003; Candrilli *et al.*, 2008**).

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 **(Goldman *et al.*, 2001; Coiffier *et al.*, 2003, Goldman, 2003**) TLS risk derives from the collective contribution of several individual risk factors and underlines the critical need for a risk model that integrates them in order to identify high TLS risk, even in unusual settings. Risk factors include: age, type of malignancy, presentation with a high initial white blood cell (WBC) count; evidence of large tumor burden (bulky disease, hepatosplenomegaly); high blood lactate dehydrogenase (LDH) (**Csako *et al*, 1982; Hande & Garrow , 1993**) or increased uric acid levels; pre-existing dehydration, oliguria, or renal failure (**Michallet** et al., **2005**).; and malignancies with high chemosensitivity(**Sparano *et al.*, 1990; Rajagopal *et al.*, 1992**).

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 (**Kedar *et al.*, 1995**). Yet patients without high-risk features may be subjected to prophylactic measures and monitoring similar to those used in patients with high-risk features. Standard preventative approaches to minimize this complication include hyperhydration, urine alkalization, xanthine oxidase inhibitors (allopurinol), and recombinant urate oxidase (**Cairo & Bishop, 2004; Davidson *et al.*, 2004**).

Some risk stratification systems have been developed by regional entities, and each system addresses different diseases, using different criteria and different thresholds for risk (**Tosi *et al.*, 2008**). One of these guidelines is the TLS risk guidelines (Bertrand **et al**, 2008) developed by the French Society for the Prevention of Cancer in Children and Adolescents (SCFE) which addressed only T-cell lymphoma, B-cell lymphoma, ALL and AML and did not assess TLS risk in adult patients. Similarly, the TLS risk stratification system developed by the Berlin–Frankfurt–Münster (BFM) Group is restricted to children (**Seidemann *et al.*, 1998; Wossmann *et al.*, 2003**) and focuses only on B-NHL and T-lymphoblastic lymphoma (T-LBL), while other guidelines proposed by an international panel of experts (**Coiffier** et al**, 2008**) do not address all malignancies or uniformly assess risk based on renal involvement. None of these guidelines can be uniformly applied to all patients at risk of developing TLS; so the need for a straightforward and unifying risk stratification model is particularly important for TLS because it is encountered almost exclusively by physicians with a haematology/oncology, nephrology and/or emergency room background (**Montesinos *et al.*, 2008**).

With the long-term aim of a risk-stratified approach to the prevention of TLS, the objectives of the current study were to describe the predictors of TLS in childhood ALL and to develop a sensitive rule to identify patients who are at risk for TLS.

2. Material and Methods:

Sixty children aged ≤18 years that were diagnosed as ALL at pediatric oncology unit and received the same line of chemotherapeutic treatment protocol were included. All the patients were diagnosed by complete blood picture, bone marrow aspirate and/or biopsy, cytochemical staining and immunophenotyping by flowcytometry (using BD FACSCalibur-flow cytometer) according to clinical and morphological characteristics including: Lymphoid Panel : T- lymphoid panel (Sm/cCD3, CD2, CD4, CD8, CD5, CD7, CD1a), B- lymphoid panel (CD19, CD22, CD20, CD10, CytIgμ, sIgμ, sIgκ , sIgλ), Others (CD23, FMC7), Myloid Panel (Anti-cMPO, CD13, CD33, CD14, CD41, anti-glycophorin A), Non lineage specific markers (HLA-DR, CD34, CD45, TdT). The patients then followed within the time frame of interest (from the date of presentation to the fifth day after initiation of chemotherapy).

Potential Predictors Evaluated

The potential predictors of TLS included laboratory features, such as white blood cells (WBC) and lactate dehydrogenase (LDH) [Initial LDH was defined as the first level obtained at admission], and clinical indicators of disease bulk, such as the presence of lymphadenopathy, hepatomegaly, and splenomegaly as assessed by the physical examination on admission. Other potential predictors examined were central nervous system (CNS) status at diagnosis and renal involvement by leukemia as inferred by renal enlargement on abdominal imaging studies, when available.

Outcomes Assessed

The primary outcome was the development of laboratory TLS, which was defined as the occurrence of any 2 or more of the following 5 laboratory abnormalities during the time frame of interest: hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, and azotemia (creatinine ≥1.5 times the age-defined upper limit of normal). Laboratory data were collected during the time frame of interest, starting from the date of presentation, through to the day of chemotherapy

initiation (Day 0), and for each of the following 5 days (Day +5).

Statistical analysis:

Statistical analysis including mean values and their standard deviations, were calculated for each variable under study using the Statistical Package for Social Sciences for windows (SPSS) version 11.0. Statistical comparison between groups was performed through Student's *t* -test.

Predictors of TLS were determined using univariate logistic regression analyses.Results are summarized as the Odds ratio, 95% confidence interval, and P-value. P values of < 0.05 were considered significant, and highly significant at *P* <0.01.

3. Results

Sixty patients were included, their demographics, and clinical features are shown in Table 1. No CNS or renal involvement encountered by laboratory and radiological examination at presentation in our study group.

Table 2 shows the laboratory abnormalities in the studied population from the date of presentation to 5 days after intiation of chemotherapy. TLS, [which was defined as the presence of at least 2 laboratory abnormalities during the time frame of interest] occurred in 27 of 60 children (45%). The single laboratory abnormality encountered most often was hypocalcemia (39 of 60 patients; 65%), whereas the least frequent abnormality was azotemia (9 of 60 patients; 15%). The most common laboratory abnormality pair for TLS was hypocalcemia and hyperuricemia (21 of 60 patients; 35%), followed by concurrent abnormalities of calcium and phosphate and hyperphosphatemia and hyperuricemia (30% for both), where combined hyperkalemia and azotemia was observed in only (5%) (Table 2). The peak laboratory values of potassium, phosphate, uric acid, and creatinine as well as the nadir of calcium and the day on which these peaks/nadirs occurred are shown in (Table 3). Comparison between those laboratory values in patients with and without TLS are shwon in (Table 3).

Predictor factors that were associated with TLS include male sex, age ≥ 10 yrs, splenomegaly, hepatomegaly, lymphadenopathy, intial WBC ≥ 20 x10/L, intial LDH ≥ 1000 IU/L and T-cell immunophenotyping, univariate logistic regression analyses of these factors are shown in table 4. All cases 27/27 (100%) developed TLS presented with high intial WBC ≥ 20 x10/L. T-cell immunophenotyping was the strongest predictor of TLS (odds ratio [OR], 8.0; 95% confidence interval; [95% CI], 1.9-32.7; *P* = .0002) and followed by intial LDH ≥ 1000 IU/L (OR, 5.0; 95% CI, 1.2-20.9; *P* = .0002).

Table 1. Study Population

Characteristic	**No. of patients (%), N = 60**
Sex	
Male	48(80)
Female	12(20)
Acute lymphoblastic leukemia immunophenotype	
B-cell :	45 (75)
Early pre- B	*6(13)*
Pre-B	*20(44)*
Common- B	*16 (36)*
Mature -B	*3(7)*
T-cell:	15 (25)
Early -T	*6(40)*
Intermediate-T	*3(20)*
Mature - T	*6(40)*
Lymphadenopathy	33(55)
Hepatomegaly	30(50)
Splenomegaly	36(60)

Table 2. Laboratory Abnormalities in Childhood Acute Lymphoblastic Leukemia From the Date of Presentation to Day +5:

Laboratory parameter	**No. of patients (%), N = 60**
Hypocalcemia	39(65)
Hyperuricemia	24 (40)
Hyperphosphatemia	21 (35)
Hyperkalemia	15(25)
Azotemia	9(15)
Hypocalcemia and hyperuricemia	21 (35)
Hypocalcemia and hyperphosphatemia	18 (30)
Hyperphosphatemia and hyperuricemia	18 (30)
Hyperkalemia and hyperuricemia	15 (25)
Hyperkalemia and hypocalcemia	12 (20)
Hyperkalemia and hyperphosphatemia	12 (20)
Hypocalcemia and azotemia	9 (15)
Hyperphosphatemia and azotemia	9 (15)
Hyperuricemia and azotemia	9 (15)
Hyperkalemia and azotemia	3(5)

Table 3. Laboratory Abnormality in patients with and without TLS and Time Relative to Chemotherapy Initiation.

Laboratory parameter	TLS present, N = 27		TLS absent, N = 33		*P*
	Mean	± SD	Mean	± SD	
Potassium peak, mmol/L	4.9	±0.5	4.2	±0.4	.02*
Phosphate peak, mg/dl	6.4	±1.3	4.3	±0.5	.001**
Calcium nadir, mg/dl	7.3	±0.8	8.7	±0.5	.005**
Uric acid peak, mg/dl	9.1	±2.5	5.4	±0.9	.004**
Creatinine peak, mg/dl	1.5	±0.4	1.0	±0.2	.03*
Mean day to potassium peak*	3.3	±0.7	2.5	±1.2	.04*
Mean day to phosphate peak*	3.0	±1.0	2.1	±1.4	.2
Mean day to calcium nadir*	2.3	±0.9	1.5	±0.5	.02*
Mean day to uric acid peak*	3.2	±0.7	2.0	±1.3	.05
Mean day to creatinine peak*	3.1	±1.2	2.3	±1.1	.2

*TLS = tumor lysis syndrome; SD= standard Deviation; * = significant; ** highly significant.

Table 4. Predictors of Tumor Lysis Syndrome by Univariate Analysis

Variable	No. of patients (%)		OR	95% CI	*P*
	TLS present (N = 27)	TLS absent (N = 33)			
Male sex	24(89)	24(73)	3	0.7-12.5	0.08
Female sex	3(11)	9(27)	0.3	0.1-1.4	0.08
Age ≥10 y	9(33)	9(27)	1.3	0.4-4.0	0.2
Splenomegaly	21(78)	15(45)	4.2	1.4-13.1	0.008**
Hepatomegaly	18(67)	12(36)	3.5	1.2-10.2	0.01*
Lymphadenopathy	15(56)	18(54)	1	0.4-2.9	0.2
Initial WBC ≥20×10^9/L	27(100)	9(27)	1.2***		<.0001**
Initial LDH ≥1000 IU/L	9(33)	3(9)	5	1.2-20.9	0.02*
T-cell immunophenotype	12(44)	3(9)	8	1.9-32.7	0.002**
B-cell immunophenotype	15(56)	30(91)	0.1	0.03-0.5	0.002**

*TLS = tumor lysis syndrome; OR= odds ratio; 95% CI=95% confidence interval; WBC= white blood count; LDH= lactate dehydrogenase.
***Variance of Haldane. *P* value from univariate logistic regression analyses. * = significant; ** highly significant.

Six cases out of 60 (10%) were considered low risk TLS group (which was defined by the absence of all 4 predictors of TLS). Of those who fulfilled low-risk TLS criteria, none of them develop TLS.

4. Discussion

Tumor lysis syndrome (TLS) is potentially life-threatening metabolic disorders which are associated with lymphoproliferative malignancies that occurs when tumor cells undergo rapid decomposition spontaneously or in response to cytoreductive therapy (**Cairo *et al.*, 2010**). Delayed recognition of the metabolic imbalances caused by the massive release of tumor cell contents may result in clinical complications such as acute kidney injury, seizures, and cardiac arrhythmias. The key principle in TLS management relies on the identification of patients at risk for developing TLS during chemotherapy or because of disease progression (**Coiffier *et al.*, 2008**). TLS-related risk factors pertain to tumor type (particularly hematologic malignancies), specific tumor characteristics (e.g. bulky tumor, high cellular proliferation rate, sensitivity to cytoreductive therapy), and other host-related factors (**Truong *et al.*, 2007**). A comprehensive grading system proposed by Cairo and Bishop, 2004 classifies TLS syndromes into laboratory or clinical TLS, thus facilitating TLS prevention and management. The mainstays of TLS management include monitoring of electrolyte abnormalities, vigorous hydration, prophylactic antihyperuricemic therapy with allopurinol, and rasburicase treatment of patients at high TLS risk or

with established hyperuricemia (**Bosly *et al.*, 2003**). Urine alkalinization in an attempt to increase uric acid solubility and use of diuretics remain controversial (**Mughal *et al.*, 2010**). Titration of sodium bicarbonate infusions to maintain a urine pH between 6.5 and 7.5 is a burden to nursing staff, whereas calcium-phosphate precipitation and subsequent nephrocalcinosis is more likely in alkali settings (**Davidson *et al.*, 2004**). Furthermore, over-alkalinization may lead to precipitation of uric acid precursors, such as hypoxanthine or xanthine (**Jones *et al.*, 1995**). Although urine alkalization still is considered the standard of care in many institutions and treatment protocols (**Albano *et al.*, 2004**) the ability to stop this maneuver in a low-risk group of children would be beneficial. In addition, although it is demonstrably effective at lowering uric acid levels and eliminating the need for alkalinization, urate oxidase is very expensive (**Calvo-Villas *et al.*, 2008**); and the definition of a low-risk group would be valuable to help avoid that unnecessary expense and the rare but real risk of hemolysis in glucose-6-phosphate dehydrogenase-deficient patients (**Kopecna *et al.*, 2002**).

There is no clear prediction for the development of TLS that could enable early detection of manifestation of this severe condition yet. Recent studies define a subgroup of patients at higher risk of renal failure during induction chemotherapy to standardize this clinical gestalt and further reduce TLS preventative measures (such as alkalinization) and limit laboratory monitoring in the low-risk population (**Cairo *et al.*, 2010**).

By using a very inclusive definition of TLS, Truong and coworkers, 2007 observed that the prevalence of TLS in children with ALL before and within 1 week of chemotherapy initiation was 23%. They the absence of 4 independent risk factors at presentation (age ≥10 years, splenomegaly, mediastinal mass, and initial WBC $\geq 20 \times 10^9$/L) to develop a prediction rule for identifying those at low risk of TLS. In the absence of all 4 factors, there was a 97% probability that TLS would not occur; and, those cases that did occur were relatively mild, were identified early, and did not require significant interventions.

We found that the strongest predictors for TLS was the presentation with high intial WBC ≥ 20 x10/L, followed by T-cell immunophenotyping (OR, 8.0; 95% CI, 1.9-32.7; P = .0002) and then intial LDH ≥ 1000 IU/L, and splenomegaly (OR, 5.0; 95% CI, 1.2-20.9; P = .0002; OR, 4.0; 95% CI, 1.4-13.1; P = .008 respectively). In our study six cases out of 60 (10%) were considered low risk TLS group none of them develop TLS. The mean peak values of potassium, phosphate, uric acid, and creatinine as well as the nadir of calcium were different between patients with and without TLS in this study and this difference was statistically highly significant as regard phosphate, uric acid, and calcium ($P<0.01$), and statistically significant for potassium and creatinine level ($P<0.05$).

These prediction rules should be applied at the time of initial hospital presentation, thus enabling the early identification of a group of children at low risk for developing TLS who may be candidates for less intensive TLS monitoring and prophylactic interventions. Reducing the frequency of unnecessary laboratory monitoring would minimize trauma to young patients.

We conclude that children with ALL who are at low risk for TLS can be identified early at the time of hospital presentation and may benefit from a risk-stratified approach directed at reduced intensity of laboratory monitoring and limited TLS prophylactic measures.

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