ARTICLE

Factors Associated with the Development of Tumor Lysis Syndrome Among Pediatric Cancer Patients at the Philippine Children's Medical Center

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BACKGROUND: Tumor lysis syndrome (TLS) is an oncologic emergency resulting from cancer chemotherapy; delays in its recognition could be life-threatening. Early recognition of associated risk factors and its management may help prevent its occurence.

OBJECTIVES: To identify the risk factors for TLS among cancer patients at the Philippine Children's Medical Center.

METHODS: This was a retrospective case-control study. Categorical variables were compared using chi-square test and continuous variables were compared using independent t-test. The association between TLS and patients' characteristics was determined through logistic regression analysis.

RESULTS: Medical records of 712 patients with cancer seen between 2016-2020 were reviewed. Children with (n=35) and without (n=137) TLS were selected as cases and controls and matched for age and cancer type. Factors associated with TLS are underweight patients with BMI < 18.5 (cOR 0.33, 95% CI 0.11-0.98); patients with both hepatomegaly and splenomegaly were four times more likely to develop TLS (cOR 3.946, 95% CI 1.2-12.94) while patients with lymphadenopathy were twice more likely to develop TLS (cOR 2.309, 95% CI 1.02-5.21). Patients with elevated WBC, low phosphorus and high uric acid at baseline have increased odds of developing TLS.

CONCLUSIONS: After group matching for age and cancer type, factors associated with increased odds of TLS among pediatric cancer patients in PCMC are hepatosplenomegaly, lymphadenopathy, elevated WBC, low potassium level, low phosphorus and high uric acid at baseline with higher fluid balance.

KEYWORDS: *tumor lysis syndrome, pediatric cancer, risk factors for TLS*

INTRODUCTION

Tumor lysis syndrome (TLS) is an oncologic emergency characterized by a group of metabolic derangements caused by the massive and abrupt release of cellular components into the blood following the rapid lysis of malignant cells. [(1)] The consequences of these derangements are potentially severe and include acute kidney injury, cardiac arrhythmias, seizures and even death. [(2)]

Tumor lysis syndrome can be diagnosed using the Cairo-Bishop Definition of TLS, which was developed in 2004. It can occur spontaneously or after starting chemotherapy. There are two types: clinical tumor lysis syndrome (CTLS) and laboratory tumor lysis syndrome (LTLS). Laboratory tumor lysis syndrome is diagnosed with the presence of two or more of the following abnormalities in a patient with cancer or undergoing treatment for cancer within 3 days prior to and up to 7 days after the initiation of

treatment: uric acid ≥ 476 umol/L or 25% increase from baseline, potassium ≥6 mmol/L or 25% increase from baseline, phosphorus ≥2.1 mmol/l or 25% increase from baseline and calcium ≤1.75 mmol/l or 25% decrease from baseline. Clinical tumor lysis syndrome on the other hand is diagnosed when a patient with laboratory tumor lysis syndrome has at least 1 of the following: creatinine ≥1.5x the upper limit of normal, cardiac arrhythmia, sudden death and seizure. [2]

The incidence of TLS is higher among hematologic malignancies, because of high rate of cell turnover and sensitivity to cytotoxic therapies. [3] It has been classically associated with bulky and rapidly dividing hematologic malignancies occurring most frequently in high-grade Non-Hodgkin Lymphoma and acute leukemia and less commonly in chronic leukemia and multiple myeloma. [4] There is a reported incidence of 5.2 to 23% in patients with Acute lymphocytic leukemia, 18% in AML with white blood cell count >75,000 and 26.4% B-cell acute lymphoblastic leukemia. [5]

In solid tumors, case reports of TLS have become increasingly common over the previous decade and are mostly seen in adult cases, although there are very limited data available in the pediatric population. Spontaneous TLS in solid tumors has been observed in the following: breast cancer, gastric cancer, germ cell tumors, gastrointestinal adenocarcinoma, squamous cell lung cancer, and metastatic castrate-resistant prostate cancer. [6]

Prevention is the best treatment for TLS. Treatment and prevention include hypouricemic agents, electrolyte management and adequate hydration. Patients who will not respond to hydration and medical management may need renal replacement therapy. [4] Intractable fluid overload, hyperkalemia, hyperuricemia, hyperphosphatemia, or hypocalcemia and renal failure are indications for renal dialysis. [2]

This study aims to identify patients who are at risk for the development of tumor lysis syndrome in hematologic malignancies and solid tumors so that prophylactic measures may be implemented before the initiation of therapy, to minimize the clinical consequences of tumor lysis syndrome. [1]

METHODOLOGY

This case control study was performed to determine the factors associated with the development of tumor lysis syndrome in children with cancer. It was conducted at the Philippine Children's Medical Center, a tertiary pediatric hospital in Quezon Avenue, Quezon City. It included all patients who were newly diagnosed to have either hematologic or solid tumor malignancy from January 2016 to December 31, 2020. Patients who started chemotherapy prior to admission at our institution were excluded. Initial laboratory results of white blood cell count, serum lactate dehydrogenase, calcium, potassium, phosphorus, uric acid and creatinine were recorded.

The diagnosis of tumor lysis syndrome was based on the Cairo-Bishop criteria. Laboratory tumor lysis syndrome was diagnosed in the presence of two or more of the following laboratory abnormalities within 3 days prior and up to 7 days after the initiation of treatment: uric acid ≥476 umol/L or 25% increase from baseline, potassium ≥6 mmol/L or 25% increase from baseline, phosphorus ≥2.1 mmol/L or 25% increase from baseline and calcium ≤1.75 mmol/L or 25% decrease from baseline.

Clinical tumor lysis syndrome on the other hand was diagnosed when a patient with laboratory tumor lysis syndrome has at least 1 of the following: creatinine ≥1.5x the upper limit of normal, cardiac arrhythmia, sudden death and seizure. Data on patients who fulfilled the criteria for TLS were collated and analyzed. Charts with incomplete data were excluded from the study.

All charts of admitted patients with newly diagnosed hematologic malignancy and solid tumor were retrieved and included in the study. The patients' charts were reviewed and the following demographic and clinical data were recorded: age, sex, weight, height, BMI (for patients above 6 years old), type of malignancy, initial and subsequent laboratory results up to 7 days after starting chemotherapy of white blood cell count, serum potassium, calcium, uric acid, phosphorus, creatinine as requested by hematologist-oncologist and/or nephrologist-in-charge. For solid tumors, the size and location as well as presence or absence of metastasis, enlarged palpable lymph nodes and their location by physical examination were noted. For hematologic malignancies, presence of enlarged palpable nodes and their distribution, presence or absence of mediastinal mass, organomegaly based on physical examination and/or imaging upon admission were recorded. Clinical monitoring for kidney function status such as daily urine output and fluid balance aside from the aforementioned laboratory parameters were also documented. Details of management such as chemotherapy or medications, method of hydration and further interventions with their corresponding outcomes were likewise collated.

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. Odds ratios and the corresponding 95% confidence intervals from Firth logistic regression were computed to determine the association between patient profile and TLS. Fisher's exact test was used to compare outcomes of those with TLS vs without TLS. All valid data were included in the analysis. Missing data were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

RESULTS

A total of 712 charts of new patients with malignancy were reviewed. Children with (n=35) and without (n=137) TLS were selected as cases and controls, respectively, with group matching for age and cancer type (Table 1). The group matching was based on data that TLS occurs more frequently in hematologic malignancies than in solid tumors. The highest risk of developing TLS is observed in patients with lymphoproliferative disorders with high proliferative rates and high tumor sensitivity to chemotherapy. [4,7] Age was also used to match patients since most malignancies are classified as high risk for patients aged 10 years and above this was done to minimize confounding in this comparison between TLS and non-TLS. The overall median age was 6.5 (range 0.08-18) years, and 134 (77.91%) had hematologic type of malignancy. Majority of the patients were males (60.47%) and had BMI of < 18.5 kg/m^2 (61.86%).

Among the hematologic types of malignancy, the three most common subtypes were B- cell acute lymphocytic leukemia, ALL (37.75%), acute

myelogenous leukemia, AML (13.95%) and T-cell acute lymphocytic leukemia, ALL (9.88%). Hepatoblastoma was the most common type of solid tumor (4.65%). Sixteen (9.3%) had a mediastinal mass. Hepatomegaly and splenomegaly were found in 72 (41.86%) and 10 (5.81%) patients, respectively while 14 (8.14%) patients had both. Cancer had metastasized to the brain in 3 (1.7%) and to other sites in 8 (4.65%) patients.

The following profiles were associated with TLS as shown in table 1: Patients who were underweight or BMI < 18.5 with a cOR 0.33, 95% CI 0.11 -0.98, p = 0.045, were more likely to develop TLS compared to patients with normal BMI. Compared to those with normal BMI, those with BMI <18.5 were less likely to have TLS (cOR 1.235, 95% CI 0.24-6.36, p = 0.801 and cOR 0.33, 95% CI 0.11-0.98, p= 0.45). There is no association with TLS and BMI for overweight or obese compared to normal BMI (cOR 1.235, 95% CI 0.24-6.36, p = 0.801 and cOR 0.529, 95% CI 0.1-2.81, p = 0.455). After matching for age and cancer type, we observed that patients with both liver and spleen organomegaly were four times more likely to develop TLS (cOR 3.946, 95% CI 1.2-12.94, p = 0.023) while patients with palpable lymphadenopathy in either cervical, axillary or inguinal area were twice more likely to develop TLS (cOR 2.309, 95% CI 1.02-5.21, p = 0.044).

Table 1. Deamographic and clinical profile of pediatric cancer patients

	Total (n=172)	**With TLS (n=35)**	**No TLS (n=137)**	**Crude Odds Ratio (95% CI)**	**p-value**
	Median (Range); Frequency (%)				
Age, years					
<10	102 (59.3)	19 (54.29)	83 (60.58)	1.0 (Reference)	-
≥10	70 (40.7)	16 (45.71)	54 (39.42)	1.296 (0.62–2.71)	0.491
Sex					
Male	104 (60.47)	21 (60)	83 (60.58)	1.0 (Reference)	-
Female	68 (39.53)	14 (40)	54 (39.42)	1.033 (0.49–2.18)	0.932
BMI, kg/m^2 [n=97]					
<18.5	60 (61.86)	10 (43.48)	50 (67.57)	**0.33 (0.11–0.98)**	**0.045**
18.5 to 23	21 (21.65)	8 (34.78)	13 (17.57)	1.0 (Reference)	-
23 to <27.5	7 (7.22)	3 (13.04)	4 (5.41)	1.235 (0.24–6.36)	0.801
≥27.5	9 (9.28)	2 (8.7)	7 (9.46)	0.529 (0.1–2.81)	0.455
Type of malignancy					
Hematologic	134 (77.91)	29 (82.86)	105 (76.64)	1.0 (Reference)	-
Solid tumor	38 (22.09)	6 (17.14)	32 (23.36)	0.715 (0.28–1.82)	0.483
Specific type of malignancy				-	-
Hematologic	134 (77.91)	29 (82.86)	105 (76.64)		
AML	24 (13.95)	2 (5.71)	22 (16.06)		
Anaplastic large cell lymphoma	1 (0.58)	1 (2.86)	0		
APML	3 (1.74)	0	3 (2.19)		
B Cell ALL	65 (37.79)	11 (31.43)	54 (39.42)		
B Lymphoblastic lymphoma	1 (0.58)	0	1 (0.73)		
Burkitt's lymphoma	3 (1.74)	3 (8.57)	0		
CML	8 (4.65)	2 (5.71)	6 (4.38)		
Hodgkin lymphoma	5 (2.91)	0	5 (3.65)		
Infantile leukemia	1 (0.58)	0	1 (0.73)		
JMML	3 (1.74)	0	3 (2.19)		

Large B Cell lymphoma	1 (0.58)	0	1 (0.73)		
NHL	2 (1.16)	0	2 (1.46)		
T cell ALL	17 (9.88)	10 (28.57)	7 (5.11)		
Solid tumor	38 (22.09)	6 (17.14)	32 (23.36)		
Hepatoblastoma	8 (4.65)	2 (5.71)	6 (4.38)		
Medulloblastoma	1 (0.58)	0	1 (0.73)		
MMGCT	3 (1.74)	1 (2.86)	2 (1.46)		
Neuroblastoma	6 (3.49)	0	6 (4.38)		
Non-seminomatous GCT	4 (2.33)	1 (2.86)	3 (2.19)		
Osteosarcoma	2 (1.16)	0	2 (1.46)		
PNET	1 (0.58)	0	1 (0.73)		
Retinoblastoma	4 (2.33)	0	4 (2.92)		
Rhabdomyosarcoma	4 (2.33)	0	4 (2.92)		
Wilms' tumor	5 (2.91)	2 (5.71)	3 (2.19)		
Metastasis					
Brain	3 (1.74)	0	3 (2.19)	0.541 (0.03–10.72)	0.687
Liver	0	0	0	-	-
Lungs	13 (7.56)	3 (8.57)	10 (7.3)	1.308 (0.37–4.65)	0.679
Others	8 (4.65)	1 (2.86)	7 (5.11)	0.757 (0.13–4.54)	0.760
With mediastinal mass	16 (9.3)	6 (17.14)	10 (7.3)	2.676 (0.93–7.7)	0.068
Organomegaly					
None	76 (44.19)	12 (34.29)	64 (46.72)	1.0 (Reference)	-
Liver only	72 (41.86)	13 (37.14)	59 (43.07)	1.171 (0.5–2.73)	0.715
Spleen only	10 (5.81)	4 (11.43)	6 (4.38)	3.572 (0.93–13.72)	0.064
Liver and spleen	14 (8.14)	6 (17.14)	8 (5.84)	**3.946 (1.2–12.94)**	**0.023**
Lymphadenopathy (cervical, axillary and inguinal)	101 (58.72)	26 (74.29)	75 (54.74)	**2.309 (1.02–5.21)**	**0.044**

Statistical test used: Firth logistic regression

The initial laboratory readings of patients are summarized in Table 2. Majority had normal potassium (121 or 70.35%), calcium (125 or 70.35%), serum creatinine (133 or 77.33%) and phosphorus (115 or 66.86%) levels. Of the parameters, cases and controls significantly differed in terms of WBC, potassium, calcium, creatinine, and uric acid. For every unit increase in WBC, the odds of TLS increases by 0.3% (cOR 1.003, 95%CI 1.001-1.01, p = 0.006). The median baseline calcium (2.4 mmol/L vs. 2.33 mmol/L) and uric acid (745 mmol/L vs. 356 mmol/L) levels were greater in children with TLS than in those without. The odds of TLS increased more than four-fold (cOR 4.70, 95% CI 1.14-19.3) with every mmol/L rise in baseline calcium, but when categorized, there was no significant association detected. TLS odds increased by 0.5% (cOR 1.005, 95% CI 1.003-1.01) with each mmol/L increment in uric acid. The median baseline serum creatinine level (54 umol/L vs 40 umol/L) was higher while the potassium level (3.3 mmol/L vs 4.1 mmol/L) and phosphorus level (1.29 mmol/L vs 1.51 mmol/L) were lower in children with TLS than in those without. Moreover, low phosphorus levels were more frequent in children with TLS (median of 1.29 vs 1.51). Patients

with high creatinine are four times more likely to develop TLS than those with normal creatinine (cOR 4.054, 95% CI 1.69-9.75, p = 0.002). Patients with low baseline phosphorus were eight to nine times as likely to develop TLS (cOR 8.68, 95% CI 3.44-21.92, p < 0.001).

Table 2. Initial or baseline laboratory profile of pediatric cancer patients and associated with tumor lysis syndrome

	Total (n=172)	With TLS (n=35)	No TLS (n=137)	Crude Odds Ratio (95% CI)	p-value
	Median (Range)				
WBC count, x10^9/L	18.7 (0.6 to 758.2)	75.7 (3.1 to 758.2)	17.3 (0.6 to 630.9)	**1.003 (1.001–1.01)**	**0.006**
Potassium, mmol/L	4 (1.7 to 6.8)	3.3 (1.7 to 5.5)	4.1 (2.3 to 6.8)	**0.368 (0.2–0.66)**	**0.001**
Low	31 (18.02)	17 (48.57)	14 (10.22)	**8.948 (3.69–21.7)**	**<0.001**
Normal	121 (70.35)	14 (40)	107 (78.1)	1.0 (Reference)	-
High	20 (11.63)	4 (11.43)	16 (11.68)	2.022 (0.62–6.57)	0.241
Calcium, mmol/L	2.35 (1.65 to 3.49)	2.4 (1.76 to 3.49)	2.33 (1.65 to 3.43)	**4.7 (1.14–19.3)**	**0.032**
Low	23 (13.37)	3 (8.57)	20 (14.6)	0.641 (0.19–2.15)	0.472
Normal (8.4–10.2)	125 (72.67)	26 (74.29)	99 (72.26)	1.0 (Reference)	-
High	24 (13.95)	6 (17.14)	18 (13.14)	1.319 (0.49–3.55)	0.584
Serum creatinine, umol/L	43 (12 to 1051)	54 (19 to 1051)	40 (12 to 146)	**1.023 (1.01–1.04)**	**0.003**
Low	13 (7.56)	0	13 (9.49)	0.174 (0.01–3.03)	0.231
Normal	133 (77.33)	23 (65.71)	110 (80.29)	1.0 (Reference)	-
High	26 (15.12)	12 (34.29)	14 (10.22)	**4.054 (1.69–9.75)**	**0.002**
Phosphorus, mmol/L	1.5 (0.13 to 2.77)	1.29 (0.13 to 2.5)	1.51 (0.77 to 2.77)	**0.219 (0.07–0.64)**	**0.006**
Low	27 (15.7)	15 (42.86)	12 (8.76)	**8.68 (3.44–21.92)**	**<0.001**
Normal	115 (66.86)	14 (40)	101 (73.72)	1.0 (Reference)	-
High	30 (17.44)	6 (17.14)	24 (17.52)	1.857 (0.67–5.18)	0.237
Uric acid, mmol/L	383 (96 to 2379)	745 (217 to 2379)	356 (96 to 1011)	**1.005 (1.003–1.01)**	**<0.001**
LDH, U/L	1000 (45 to 51730)	2016 (337 to 51730)	970 (45 to 35480)	1 (0.99–1.0001)	0.05

Statistical test used: Firth logistic regression

Chemotherapy was given to 170 patients in the study (98.84%) and 34 (97.14%) had TLS with one patient having spontaneous tumor lysis even prior to giving of chemotherapy. There were 155 patients who received hyperhydration (90.12%) and 93 patients (54.07%) and 105 patients (61.05%) of the total were given hypouricemic agents and electrolyte management respectively; most were given in combination with each other (Table 3). Only four (11.43%) patients with TLS underwent dialysis.

Table 3. Treatments received by newly diagnosed cancer patients and their TLS

	Total (n=172)	With TLS (n=35)	No TLS (n=137)
	Frequency (%)		
Chemotherapy	170 (98.84)	34 (97.14)	136 (99.27)
Hydration	155 (90.12)	35 (100)	120 (87.59)
Hypouricemic agent	93 (54.07)	31 (88.57)	62 (45.26)
Electrolyte management	105 (61.05)	33 (94.29)	72 (52.55)
Dialysis	4 (2.33)	4 (11.43)	0

The median onset of TLS was 2 days (range 0-6) from chemotherapy initiation (Table 4). In-hospital mortality rate was greater among cases (14%) than controls (7%) but did not reach statistical significance. Patients with TLS are more likely to develop fluid overload at 499 (CI -2225-5500, p value – 0.011).

	Total (n=172)	With TLS (n=35)	No TLS (n=137)	p-value
	Median (Range); Frequency (%)			
Days from chemotherapy initiation [n=28]	[n=28] 2 (0–6)	[n=28] 2 (0–6)	-	-
Urine output during chemotherapy, cc/kg/hr	3.35 (0.11 to 12)	3.02 (0.11 to 9.1)	3.4 (1 to 12)	0.064*
Fluid balance during chemotherapy	275 (-2225 to 5500)	499 (-2225 to 5500)	200 (-540 to 2824)	**0.011***
Final status				0.192†
Alive and discharged	157 (91.28)	30 (85.71)	127 (92.7)	
Expired	15 (8.72)	5 (14.29)	10 (7.3)	

Statistical test used: * - Mann-Whitney U test; † - Fisher's exact test.

Indicators for TLS clinical and laboratory criteria are shown in Table 5. The median creatinine level in umol/L was 42 (range of 12-1051) and it was higher in patients with TLS than without (54 vs 40). Majority of the patients had normal serum creatinine levels (74.42%). Patients who had high creatinine were more likely to develop TLS as compared to those who did not develop TLS (40% vs 8.76%). One patient had cardiac arrhythmia and also one patient had seizure. Both had TLS.

About 52 (30.23%) had potassium of ≥ 6 mmol/L or at least 25% increase from baseline and majority had TLS (25 or 74.29%). The median potassium level in mmol/L was 4.2 (range of 2.2-35) and it was higher in patients with TLS than without (5 vs 4.1). Most of the patients had normal potassium levels (65.7%), and majority do not have TLS (73.72%). Eleven (6.4%) had calcium levels of ≤1.75 mmol/L or at least 25% decrease from baseline and more frequently seen in patients with TLS (28.57% vs 0.73%). The median calcium level in mmol/L was 2.2 (range of 0.62-3.49) and it was higher in patients without TLS (2.26 vs 2.08). Forty-eight (27.91%) has phosphorus levels of ≥ 2.1 mmol/L or at least 25% increase from baseline and more frequently seen in patients with TLS (91.43%). The median phosphorus level in mmol/L was 1.5 (range of 0.54-4.35) and it was higher in patients with TLS (2.26 vs 1.4). Twenty (11.63%) had uric acid >476 umol/L or at least 25% increase from baseline and it was more frequent in patients with TLS (42.86% vs 3.65%). The median uric acid in mmol/L was 245 (range of 69-1510), and it was higher in patients with TLS (434 vs 222).

Table 5. Indicators for Laboratory and Clinical TLS Criteria

	Total (n=172)	With TLS (n=35)	No TLS (n=137)
	Median (Range); Frequency (%)		
Clinical criteria (any one)			
Creatinine	42 (12–1051)	54 (19–1051)	40 (12–146)
Low	18 (10.47)	1 (2.86)	17 (12.41)
Normal	128 (74.42)	20 (57.14)	108 (78.83)
High	26 (15.12)	14 (40)	12 (8.76)
Cardiac arrhythmia	1 (0.58)	1 (2.86)	0
Sudden death	0	0	0
Seizure	1 (0.58)	1 (2.86)	0
Laboratory criteria (any two)			
Potassium ≥6 mmol/L or at least 25% increase from baseline	52 (30.23)	26 (74.29)	26 (18.98)
Potassium	4.2 (2.2–35)	5 (2.2–6.6)	4.1 (2.5–35)
Low	14 (8.14)	2 (5.71)	12 (8.76)
Normal	113 (65.7)	12 (34.29)	101 (73.72)
High	45 (26.16)	21 (60)	24 (17.52)
Calcium ≤1.75 mmol/l or at least 25% decrease from baseline	11 (6.4)	10 (28.57)	1 (0.73)
Calcium	2.25 (0.62–3.49)	2.08 (0.62–2.75)	2.26 (1.82–3.49)
Low	42 (24.42)	20 (57.14)	22 (16.06)
Normal (8.4–10.2)	116 (67.44)	12 (34.29)	104 (75.91)
High	14 (8.14)	3 (8.57)	11 (8.03)

Phosphorus ≥2.1 mmol/l or at least 25% increase from baseline	48 (27.91)	32 (91.43)	16 (11.68)
Phosphorus	1.5 (0.54–4.35)	2.26 (0.69–4.35)	1.4 (0.54–2.5)
Low			
Normal			
High			
Uric acid ≥476 umol/l or at least 25% increase from baseline	20 (11.63)	15 (42.86)	5 (3.65)
Uric acid	245 (69–1510)	434 (69–1510)	222 (75–450)
Low	32 (18.6)	3 (8.57)	29 (21.17)
Normal	98 (56.98)	7 (20)	91 (66.42)
High	42 (24.42)	25 (71.43)	17 (12.41)

Discussion

Risk factors for TLS can either be patient or tumor related. In this study, subjects were matched according to age and diagnosis i.e. hematologic malignancy versus solid oncologic tumors. It was found out that TLS is associated with the following: hepato-splenomegaly with TLS occurring four times more than those without any organomegaly; lymphadenopathy increased the odds of TLS two times more than those without. Other factors associated with developing tumor lysis syndrome were having a higher baseline WBC count as well as low potassium levels, higher creatinine, low phosphorus, high uric acid at baseline as well as higher fluid balance during the chemotherapy. On the other hand, there was decreased risk of TLS in patients with BMI of less than 18.5 (cOR 0.33 95% CI 0.11 – 0.98, p-value 0.045) compared to normal BMI range.

Patient related factors such as organomegaly and lymphadenopathy appear to significantly increase the chance of developing tumor lysis syndrome. These findings are also consistent with the findings in the study by Gopekumar et al in 2018, which analyzed the outcomes of tumor lysis syndrome in children with leukemia and lymphoma. In a univariate analysis, the presence of a mediastinal mass, generalized lymphadenopathy, hyperuricemia and hyperleukocytosis were significantly associated in the development of TLS. However, in the multivariate analysis, only the presence of hyperuricemia reached statistical significance.[8]

Laboratory features of patients who developed tumor lysis syndrome were increased serum creatinine levels as well as hyperphosphatemia.[9] However, in this study, an increased risk of TLS was observed among patients with low to normal baseline phosphorus and high baseline calcium levels.

This is similar to the 10-year review by Ahn et al. in 2011 on 396 children who were diagnosed with acute leukemia and non-Hodgkin lymphoma, which showed a four-fold increase in the risk of developing TLS in patients with hypophosphatemia.[24] This may be explained by the use of phosphorus in the synthesis of cellular components for the tumor cells to proliferate and then eventually lysed by chemotherapy causing the extracellular phosphorus to be shifted into the cancer cells thus causing hypophosphatemia. Another explanation for this may be a possible proximal tubular dysfunction from competitive inhibition of tubular reabsorption of phosphorus by some unidentified metabolites of malignant cells. Therefore, hypophosphatemia can be an indication of high tumor burden or high cell proliferation rate which is a major predictor of TLS. [10,11]

Other tumor related factors such as high baseline serum uric acid and high levels of white blood cells were also noted to have increased the risk for TLS. In this study, those who developed TLS had a median baseline white blood cell count of 75,000/mL while those who did not develop TLS had a median baseline of 17,300/mL. The elevated serum LDH level however did not show a significant increase (cOR 1, 95% CI 0.99–1.0001, p 0.05) in the risk of developing TLS. In several studies however, elevated initial levels of serum LDH that indicate tumor bulk is considered a very significant risk factor in developing TLS. [10,12,13,14] Other factors such as presence of a mediastinal mass did not increase the risk for TLS (cOR 2.676, 95% CI 0.93 – 7.7, p 0.068). These are cases of T cell ALL and Diffuse Large B-cell Lymphoma. This is in contrast to a study by Nasir et al that reported the presence of mediastinal mass as the most significant factor for mortality and tumor lysis syndrome. There were 61 children with mediastinal masses that were included in the study; 72.1% had T cell lymphoblastic leukemia with anterior mediastinal masses. [15] Numerous other studies have shown these characteristics to be significant risk factors but results of this study may suggest that these factors may not be statistically significant in this matched control study but is clinically significant.

There are more cases of TLS seen in patients with hematologic malignancies than in those with solid tumors. Among the hematologic malignancies, most were cases of ALL. As seen in Table 1, acute lymphoblastic leukemia with B cell immunophenotype followed closely by T cell immunophenotype had the most cases of TLS, which is consistent with findings of Abdel-Baser et al. in 2012 wherein, T-cell immunophenotyping was the strongest predictor of TLS.[13]

In solid tumors, tumor lysis syndrome although rare, an increase in cases has been seen recently. In a comprehensive review of literature by Findakly et al. in 2020 on tumor lysis in solid tumors in both adult and pediatric population, it was recognized that the recent advancement in cancer therapy has brought about increase in the incidence of tumor lysis in solid tumors, previously thought to be rarely associated. This observation is important because the increasing mortality in TLS from solid tumors rose to as high as 35% compared to 1.9% rate reported for patients with ALL and NHL. [16] Another review by Criscuolo et al in 2015, also showed a less frequent occurrence of tumor lysis syndrome in solid cancers, and is usually associated with bulky and high chemosensitive diseases; spontaneous events prior to chemotherapy are seen mostly as case reports. [17]

In this study, a total of 35 solid tumor cases were identified. Six (17.1%) had TLS; 2 had hepatoblastoma, 2 had Wilms' tumor, and 2 had germ cell tumors. Four of the six cases were already advanced with metastasis to the lungs and bone marrow. Solid tumors are considered low risk to develop tumor lysis syndrome as classified in Cairo Bishop and most are case reports. Although TLS is rare, cases of TLS seen in hepatoblastoma, germ cell tumors, neuroblastoma and even rhabdomyosarcoma in children have been reported. [12,16,18]

The following interventions were given to those who were assessed to have a higher risk of TLS development in pediatric cancer patients: hyperhydration, the use of hypouricemic agents and electrolyte management such as giving of aluminum magnesium oxide and phosphate-binding medication (sevelamer) for hyperphosphatemia. This practice is based on the treating physician's knowledge as guided by the Cairo-Bishop Criteria : that patients who are at high risk in developing TLS are identified and aggressive management to prevent TLS are given early in the course of treatment. Four cases out of the 35 (11%) cases with TLS progressed to acute kidney injury needing dialysis despite hyperhydration, hypouricemic agents and other oral agents. These are cases of Burkitt's lymphoma, hepatoblastoma and 2 cases of B cell ALL. All had elevated creatinine, phosphorus and uric acid with seizures and cardiac arrythmia after the giving of chemotherapy.

There were 5 deaths out of the 35 cases that had TLS (14.3%), which is higher compared to 10 out of 137 deaths (7.3%) in non-TLS patients. The causes of death were mostly multifactorial and due to multiple organ failure wherein tumor lysis syndrome may have contributed as well. In patients with no TLS, causes of death were mostly from hemorrhage (intracranial) and sepsis.

Tumor lysis syndrome developed more frequently in patients after receiving chemotherapy (31/35, 88%) than spontaneously prior to chemotherapy (4/35, 11%). With this result, it is recommended to closely monitor the levels of uric acid and serum electrolytes in patients being treated with chemotherapy. It is suggested to give aggressive hydration, electrolyte management and monitoring as early as 48 hours prior to initiating any treatment. This is also congruent with recommendations in a study by Adeyinka et al in the management tumor lysis syndrome that Intravenous fluid should be initiated 48 hours before the start of chemotherapy and should be continued for 48 hours after chemotherapy. This allows volume expansion and increase glomerular filtration rate that can help in the excretion of the solutes associated with tumor lysis syndrome. [9,15]

Conclusion and Recommendations

After group matching for age and cancer type, the following were associated with increased odds of TLS among pediatric patients with malignancy at PCMC: liver and spleen organomegaly, lymphadenopathy, elevated baseline WBC, low potassium level, low phosphorus and high uric acid at baseline with higher fluid balance on monitoring. While the following factors did not increase the odds of developing TLS: sex, elevated LDH, creatinine, presence of mediastinal mass and presence of metastasis.

The current study was limited by its retrospective nature. It did not present the actual prevalence of tumor lysis syndrome in our institution since a lot of cases were not included in the analysis

due to incomplete data. A prospective cohort study is more ideal as it will allow assessment of subjects at baseline. The data collection will be more accurate with regard to exposures, confounders and endpoints. Nonetheless, this study provided a baseline estimate for TLS cases and their profile in our institution that may be used as a comparison in further research.

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