e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(10); 975-981

Original Research Article

Clinical Profile and Biochemical Abnormalities in Tumour Lysis Syndrome Secondary to Adult Haematolymphoid Malignancies

Pankaj P. Khobragade[1], Darpan P. Jakkal[2], P.S. Jirvankar[3], Kailas N. Chintale[4]*

[1]Junior Resident-3, Department of Medical Oncology, Government Medical College & Cancer Hospital, Aurangabad, Maharashtra, India

[2]Associate Professor, Department of Medical Oncology, Government Medical College & Cancer Hospital, Aurangabad, Maharashtra, India

[3]Professor & HOD, Department of Medical Oncology, Government Medical College & Cancer Hospital, Aurangabad, Maharashtra, India

[*4]Associate Professor, Department of Medical Oncology, Government Medical College & Cancer Hospital, Aurangabad, Maharashtra, India

Received: 25-07-2023 / Revised: 28-08-2023 / Accepted: 30-09-2023

Corresponding author: Dr. Kailas N. Chintale

Conflict of interest: Nil

Abstract:

Introduction: Tumour lysis syndrome (TLS) is a metabolic complication that may follow after the initiation of anticancer therapy. It is characterized by a metabolic abnormality including hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia which occurs due to rapid lysis of tumour cells and leads to severe renal impairment, cardiac arrhythmias, or seizures and death. It is one of the oncologic emergency encounters in patients with haematological and other malignancies which may cause death. Spontaneous TLS is a rare occurrence, but it may result in more severe clinical outcomes because of the lack of benefit of pre-treatment. Drugs used for the treatment of Tumor lysis syndrome are allopurinol, febuxostat, rasburicase and supportive care.TLS patients with acute renal failure needs Hemodialysis with intensive care management.

Material and Methods: This was a cross sectional, observational and Descriptive study conducted in tertiary care centre & teaching institute during the period from December 2019 to December 2021. Total 50 patients of Adult Hematolymhooid Malignancies with diagnosis of Tumour Lysis syndrome as per Guidelines were included in this study after satisfying inclusion and exclusion criteria.

Results: The Mean ± SD of study population was 42.32 ± 18.93 years. Among all cases males were 54% and females were 46%. On distributing cases according to diagnosis of TLS, most cases were of B- ALL (32%) followed by T-ALL (24%), Burkitt's lymphoma (14%), DLBCL (14%) and CML, MM, AML, CLL 4% each. In the present study Tumor lysis patients were presented with or without signs and symptoms, few cases were presented with the following symptoms, Fatigue (6%), oliguria (10%), nausea and vomiting (6%), altered sensorium (4%), anorexia (4%) and seizures (2%). In the biochemical abnormalities LDH level was seen to be raised, more than 280 U/L in 86% cases showing significant association with Diagnosis of TLS (P value of 0.0142) serum uric acid level was significantly raised in all cases i.e. more than 7 mg/dl. Serum creatinine was found to be raised (> 1.2 mg/dl) in 66% cases. Serum calcium level was seen significantly low < 8.6 mg/dl in 61% cases with P value of 0.0252. No significant association was seen in serum phosphate level and diagnosis of TLS in this study (p value of 0.2091). Serum potassium level and Diagnosis of TLS has shown significant association with p value 0.0361.

Conclusion: Tumour lysis syndrome is a common and life-threatening event in patients with haematological malignancy undertaking chemotherapy. The incidence is increasing because of more effective cancer treatments and needs due attention in these malignancies. The early recognition and treatment of metabolic abnormalities usually prevents the severe and life-threatening complications associated with tumour lysis syndrome.

Keywords: TLS, Clinical TLS, Laboratory TLS, Adult Hematolymhoid Malignancies, Allopurinol, Febuxostat, Rasburicase.

Introduction:

Tumour lysis syndrome (TLS) is a metabolic complication that may follow after the initiation of anticancer therapy. It is characterized by a metabolic abnormality including hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia which occurs due to rapid lysis of tumour cells and leads to severe renal impairment, cardiac arrhythmias, or seizures and death. [1] It is

one of the oncologic emergency encounters in patients with haematological and other malignancies which may cause death. [2]

Spontaneous TLS is a rare occurrence but it may result in more severe clinical outcomes because of the lack of benefit of pre-treatment. [3] It is 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. It is observed most frequently in patients with haematologic malignancies such as acute lymphoblastic leukemia (ALL) and Burkitt's lymphoma after the initiation of chemotherapy, although it may also occur in other malignancies, both haematologic and solid tumours. These malignancies share the characteristics of a high proliferative rate, large tumour burden or high sensitivity to cytotoxic therapy. [4]

It is usually associated with the initiation of chemotherapy but may occur with radiotherapy, surgery, endocrine therapy, glucocorticoids; interferon, hyperthermia or spontaneously. [5] With the introduction of increasingly effective drugs and high dose chemotherapy regimens there is potentially increased risk of the development of tumour lysis syndrome because of the rapid cell breakdown. For this reason, it is also being seen in a wider range of malignant diseases. [6]

Tumour lysis leads to the release of large quantities of potassium from the cytoplasm, urate from purine degradation and phosphate from nucleoproteins into the systemic circulation. Clearance of the products of tumour lysis depends on renal excretion, hepatic metabolism and phagocytosis by the reticulo-endothelial system. Renal clearance is the primary mechanism for the excretion of uric acid, potassium and phosphate and the metabolic derangements of tumour lysis will be exacerbated by the development of renal failure. [7] The syndrome consists of laboratory abnormalities either alone (laboratory TLS) or with clinical sequelae including renal failure, seizures and arrhythmias (clinical TLS).

Clinical TLS is a predictor for worse overall morbidity and mortality in cancer patients, but can be prevented. Thus, accurate prognostication is critical to appropriate management of patients at risk for TLS and incorporates both disease factors (tumour type and burden) and patient factors (baseline renal insufficiency or hyperuricaemia). Strategies to prevent TLS include hydration and allopurinol in low and intermediate risk patients and rasburicaase in high-risk patients. [8] The modern definition of TLS is based on the Cairo–Bishop criteria for laboratory and clinical TLS. Laboratory TLS is defined as either a 25% change from baseline or an abnormal change in two of the following electrolyte/metabolite levels: uric acid, potassium or phosphorus (elevations) and calcium (decrease). Clinical TLS is simply defined as laboratory TLS with the addition of an elevated creatinine (at least 1.5 times the upper limit of normal) not attributable to another cause, cardiac arrhythmia/sudden death or seizures. Given newer treatment/preventive measures, both forms of TLS may have clinical implications. [8] As the data of Tumour lysis syndrome is very scarce so this present study is aimed to highlight clinical profile and biochemical abnormalities in cases of Tumour lysis Syndrome.

Table 1 Cairo-Bishop Laboratory and Clinical Diagnostic Criteria for Tumor Lysis Syndrome

Laboratory TLS (≥2 present)	Clinical TLS (≥1 present)
Uric acid ≥8 mg/dL, or 25% increase from baseline	Creatinine >1.5 times the upper limit of normal
Potassium ≥6 mmol/L, or 25% increase from baseline	Cardiac arrhythmia/sudden death
Phosphorus ≥4.5 mg/dL (adults), or 25% increase from baseline	Seizure
Calcium <7 mg/dL, or 25% decrease from baseline	

TLS indicates tumor lysis syndrome.
Sources: Parsi M, et al. *Cureus*. 2019;11:e6186[5]; Cairo MS, Bishop M. *Br J Haematol*. 2004;127:3-11.[6]

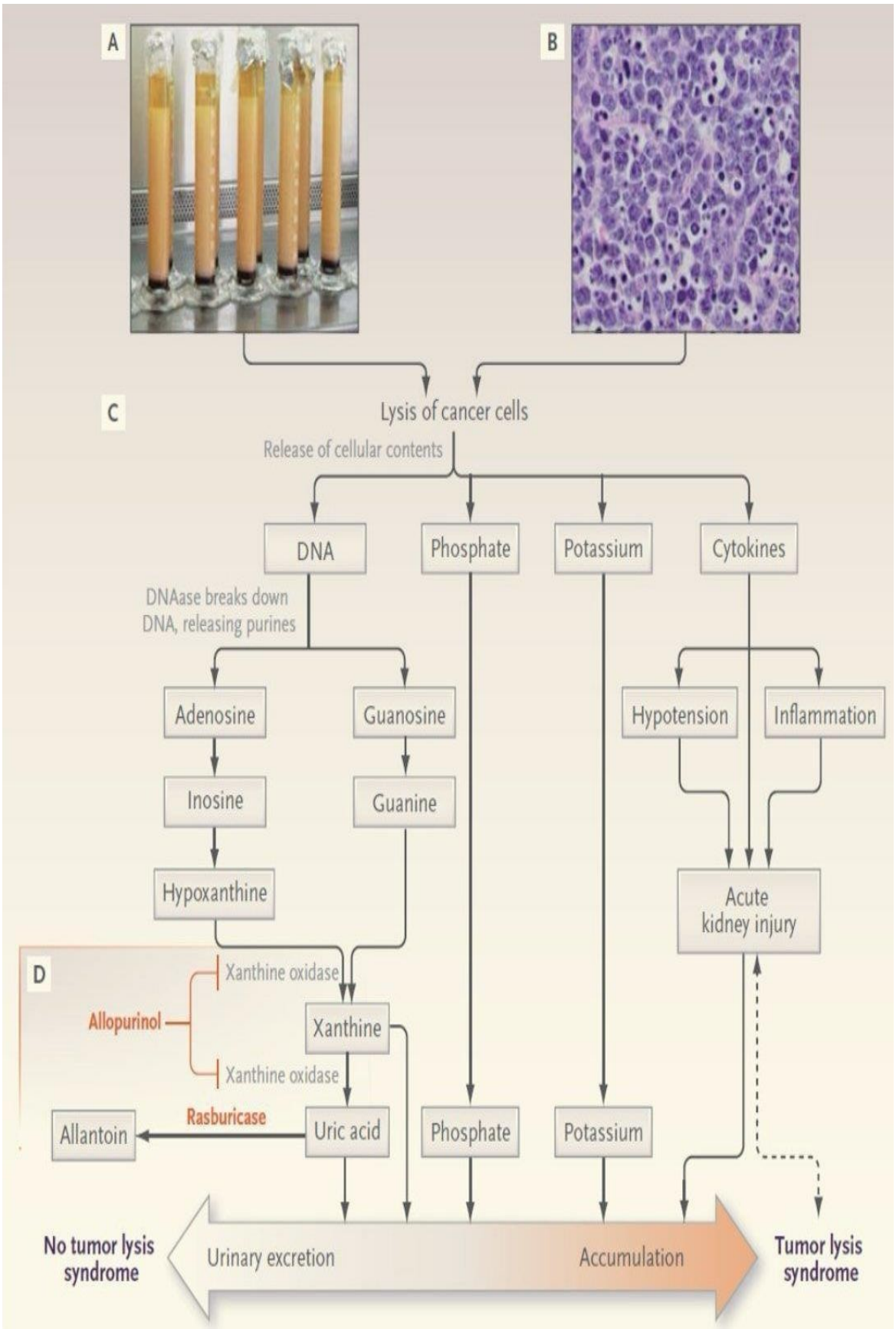

Figure 1: Mechanism of Lysis of tumour cells and release of DNA, Phosphate, Potassium and Cytokines

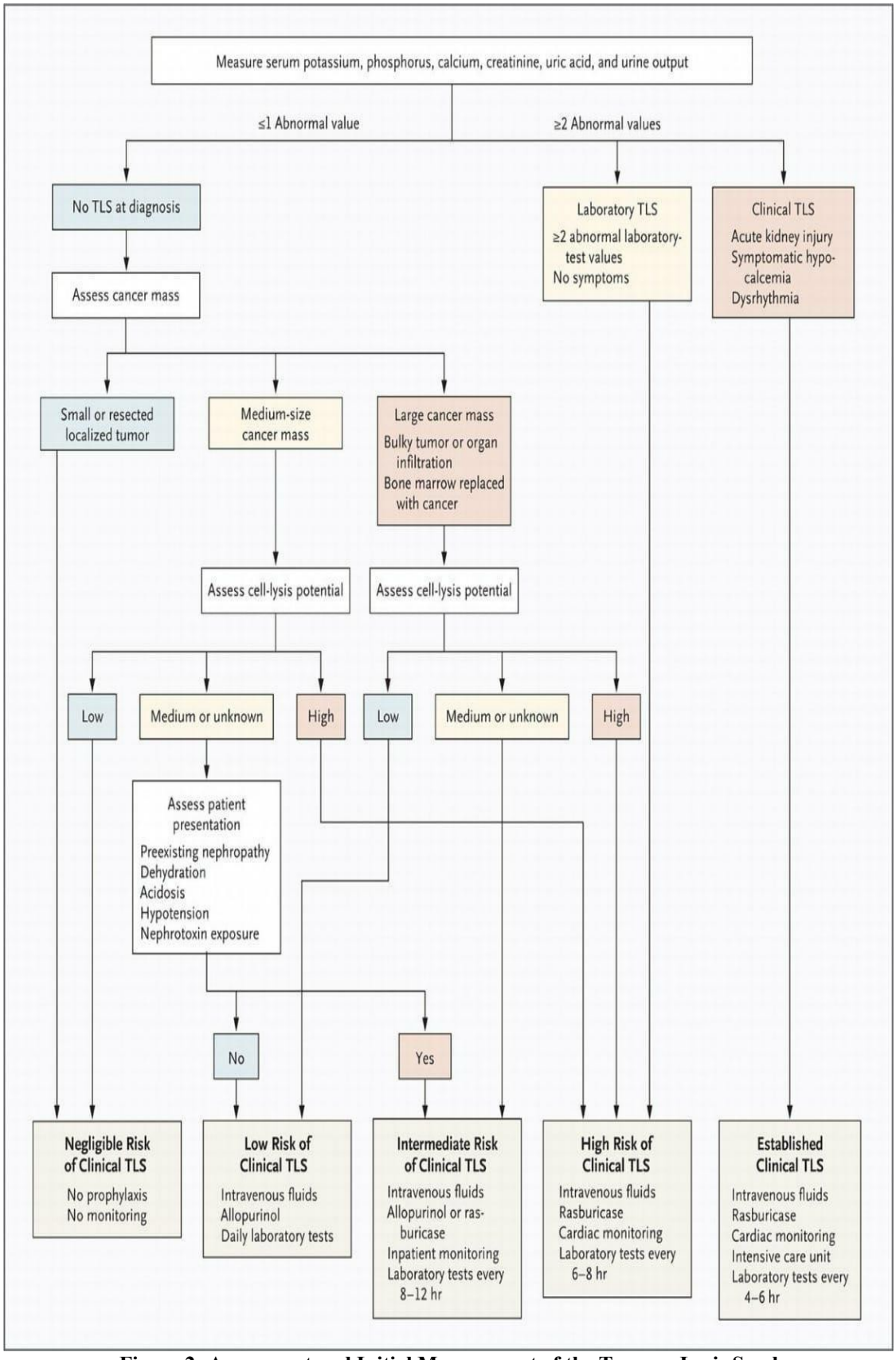

Figure 2: Assessment and Initial Management of the Tumour Lysis Syndrome

Material and Methods:

This was a cross-sectional, observational and Descriptive study conducted in tertiary care centre & teaching institute during the period from December 2019 to December 2021.

This study was started after getting valid written permission from institutional ethical committee; Total 50 patients of Adult Hematolymhooid Malignancies with diagnosis of Tumour Lysis syndrome were included in this study after satisfying inclusion and exclusion criteria.

All patients of Haematolymphoid malignancies with features of tumour lysis syndrome were enrolled in this study. They were divided into two categories- 1) Laboratory defined Tumour lysis Syndrome and 2) Clinical Tumour lysis Syndrome. Inclusion Criteria were Age >12 years of age and Patient with haematolymphoid malignancies who fulfil the criteria of Tumour lysis Syndrome. Exclusion criteria were Patients not giving informed consent, Patients who has received anti-Tumour lysis Syndrome measures outside the hospital and Patients with concurrent renal comorbidities**.** Information was collected using a preformed proforma.

Detail Procedure of study:

All patients of Haematolymphoid malignancies with features of tumour lysis syndrome were enrolled in this study as per inclusion and exclusion criteria. They were divided into two categories laboratory-defined Tumour lysis Syndrome and Clinical Tumour lysis Syndrome.

Selected patients were admitted to medical oncology wards and intensive care unit after admission detailed clinical history was taken from Each and every case, detailed clinical examination was done and Routine blood investigations were done as per preformed proforma of the present study. Vitals were taken on admission and regularly during the course of treatment. After admission following investigations were done for the diagnosis and management of tumour lysis syndrome patients i.e. complete blood count, Peripheral smear, Serum electrolytes, Serum calcium level, Serum uric acid level, Serum LDH level, Serum phosphorus level, serum creatinine, Random blood sugar, Arterial blood gases as and when required, Electrocardiogram, Liver function tests, Kidney Function Tests and other relevant investigations were done as per diagnosis and clinical condition of patients as and when required. Monitoring of patients was done in ICU.

Results:

Table 2: Distribution of cases according to diagnosis

Diagnosis	No. of Patients	Percentage (%)
B-ALL	16	32
T-ALL	12	24
Burkitt's Lymphoma	7	14
DLBCL	7	14
CML	2	4
MM	2	4
AML	2	4
CLL	2	4
Total	50	100

On distributing cases according to diagnosis of TLS, most cases were of B- ALL (32%) followed by T-ALL (24%), Burkitt's lymphoma (14%), DLBCL (14%) and CML, MM, AML, CLL 4% each.

Table 3: Distribution of cases according to diagnosis and clinical features

Diagnosis	Fatigue	Oliguria	Nausea & Vomiting	Altered sensorium	Anorexia	Seizures
DLBCL	-	-	-	-	-	-
CML	-	-	-	-	-	-
Burkitt's Lymphoma	1	1	-	-	-	-
T-ALL	1	3	1	-	-	1
MM	-	-	-	-	-	-
AML	-	-	-	1	-	-
CLL	-	1	1	-	-	-
B-ALL	1	-	1	-	2	-
Total	3 (6%)	5 (10%)	3 (6%)	1 (2%)	2(4%)	1 (2%)

In the present study, Tumor lysis patients were presented with or without signs and symptoms, few cases were presented with following symptoms, Fatigue (6%), oliguria (10%), nausea and vomiting (6%), altered sensorium (4%), anorexia (4%), seizures (2%).

Discussion:

We analysed 50 patients of Adult hematolymhoid malignancy who developed tumour lysis syndrome and we studied clinical profile and biochemical abnormalities in those patients.

Among the 50 study cases 38% patients were from 18 to 30 years of age group. 12% were from 31 to 40, 16% from 41 to 50, 10% from 51 to 60, 22% from 61 to 70 and 2% were from above 70 years age group. The Mean ± SD of age was 42.32 ± 18.93. While the median age was 41 years. In this study 54% cases were males while 46% were females. On distribution of study cases according to diagnosis we had observed that 14% study cases were of DLBCL, CML patients 4%, Burkitt's lymphoma patients 14%, T ALL patients 24%, MM patients 4%, AML patients 4%,, CLL patients 4%, B ALL patients 32%.Findings of similar studies are given below. Laboratory investigations were done to detect biochemical abnormalities.

Table 4: Comparison of incidence of haematological malignancies in Different studies with the present study

Diagnosis	Present Study	Nauffal M et al[11]	Samet Yaman et al[10]
DLBCL	7	-	18
CML	2	3	10
Burkitt's Lymphoma	7	-	7
T-ALL	12	6	7
MM	2	15	10
AML	2	16	15
CLL	2	-	-
B- ALL	16	-	-

On distributing LDH level of cases according to diagnosis we had observed that in most of the (86%) cases LDH level was more than 280 U/L. While in remaining 14% of cases it was between 140 to 280 U/L. In the present study mean LDH level was 1568 U/L while the median was 956 U/L. In similar studies conducted by Samet Yaman et al and Kukkar et al mean LDH level was 477 U/L and 299.94 U/L respectively, in study conducted by Nauffal M et al median LDH level was 892 U/L. on distributing uric acid level of cases according to diagnosis we observed that in 100% cases uric acid level was more than 7 mg/dl. In the present study mean uric acid level was 15.3 mg/dl and median were 14.50 mg/dl. In similar studies conducted by Samet Yaman et al and Kukkar et al mean uric acid level was 13.27mg/dl and 18.1 mg/dl respectively, in study conducted by Nauffal M et al median uric acid level was 17.3mg/dl.

On distribution of creatinine level of cases according to diagnosis showed that, in 66% cases serum creatinine level was more than 1.2 mg/dl. Remaining 32% had serum creatinine in between 0.5 to 1.2 mg/dl and 2% had below 0.5 mg/dl. In the present study mean creatinine level was 1.33 mg/dl and median was 1.5 mg/dl. In similar studies conducted by Samet Yaman et al and Kukkar et al [mean] creatinine level was 2.16 mg/dl and 3.28 mg/dl respectively, in study conducted by Nauffal M et al median creatinine level was 3.96 mg/dl. We had distributed cases according to serum calcium level according to diagnosis. We found that in 62% cases serum calcium level was below 8.6 mg/dl, in 30% cases serum calcium level was in between 8.6 to 10.3 mg/dl while in 8% cases it was more than 10.3 mg/dl. In present study mean calcium level was 8.57 mg/dl and median was 8.4 mg/dl. In similar studies conducted by Samet Yaman et al mean calcium level was 8.53 mg/dl, in study conducted by Nauffal M et al median calcium level was 9.1 mg/dl.

On distributing phosphate level of cases according to diagnosis we observed that in most of the (58%) cases serum phosphate level was more than 4.5 mg/dl. In remaining 38% it was between 3 to 4.5 mg/dl and in 14% it was less than 3 mg/dl. In present study mean serum phosphate level was 4.86 mg/dl and median was 4.86 mg/dl. In similar studies conducted by Samet Yaman et al mean phosphate level was 4.8 mg/dl, in study conducted by Nauffal M et al median phosphate level was 5.7 mg/dl.

On distributing serum potassium level of cases according to diagnosis we observed that in most of the 60% cases serum potassium level was in between 3.6 to 5.2 mg/dl. In remaining 22% it was more than 5.2 mg/dl and in 18% it was less than 3.6 mg/dl. In present study the mean serum potassium level was 4.53 mg/dl while the median was 4.35 mg/dl. In a study conducted by Samet Yaman et al the mean potassium level was 4.53 mg/dl. The results of the present study are consistent with the previous studies.

Summary:

1. The Mean ± SD of study population was 42.32 ± 18.93 years.
2. Among all study cases males were 54% and females were 46%.
3. On distributing study cases according to diagnosis of TLS, most of study cases were of B- ALL (32%) followed by T-ALL (24%), Burkitt's lymphoma (14%), DLBCL (14%) and CML, MM, AML, CLL 4% each.

4. In present study Tumor lysis patients were presented with or without signs and symptoms, few cases were presented with following symptoms, Fatigue (6%), oliguria (10%), nausea and vomiting (6%), altered sensorium (4%), anorexia (4%), seizures (2%).
5. In the biochemical abnormalities, LDH level was seen to be raised in more than 280 U/L in 86% study cases showing significant association with Diagnosis of TLS (P value 0.0142)
6. Uric acid level was significantly raised in all study cases i.e. more than 7 mg/dl.
7. Serum creatinine was found to be raised (> 1.2 mg/dl) in 66% study cases.
8. Serum calcium level was seen significantly low < 8.6 mg/dl in 61% study cases with P value 0.0252.
9. No significant association was seen in serum phosphate level and diagnosis of TLS in this study (p value 0.2091).
10. Serum potassium level and Diagnosis of TLS has shown significant association with p value 0.0361.
11. 37 patients were of laboratory TLS and 13 patients were of clinical TLS.
12. Injection Rasburicase and Tablet febuxostat, Allopurinol were used as per guidelines for treatment of tumour lysis syndrome with supportive treatment.
13. 32 patients of Aggressive haematolymhoid malignancies had developed tumour lysis syndrome at the onset of Presentation and 18 patients developed tumour lysis syndrome after the initiation of chemotherapy.
14. TLS Mortality was seen in 10 % (5 Deaths).

Conclusion:

Tumour lysis syndrome is a common and life-threatening event in patients with haematological malignancy undertaking chemotherapy. The incidence is increasing because of more effective cancer treatments and needs due attention in these malignancies. There must be standard and universally accepted diagnostic criteria for TLS to start therapy immediately, to correct all biochemical parameters before cancer treatment, to assess risk level of patients for TLS and to select treatment options based on the risk level. Successful management and treatment of tumour lysis syndrome is highly dependent on the prompt identification of biochemical abnormalities, signs and symptoms of patients at risk. The early recognition and treatment of metabolic abnormalities usually prevents the severe and life-threatening complications associated with tumour lysis syndrome.

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