A STUDY TO DETERMINE THE INCIDENCE OF CHEMOTHERAPY - RELATED TUMOUR LYSIS SYNDROME AT KENYATTA NATIONAL HOSPITAL

A DISSERTATION SUBMITTED AS PART FULLFILLMENT OF REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE IN INTERNAL MEDICINE. UNIVERSITY OF NAIROBI

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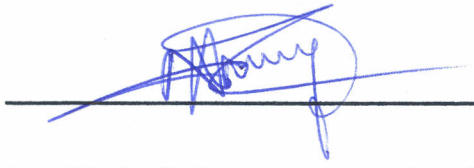
DECLARATION

I certify that this dissertation is my own original work and has not been presented for a degree at any other university.



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DEDICATION

This study is dedicated to all cancer patients and all the people with interest in cancer treatment.

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LIST OF ABBREVIATIONS AND ACRONYMS

ARF---------- Acute Renal Failure

BUN----------Blood Urea Nitrogen

CRF----------Chronic Renal Failure

GFR----------Glomerular Filtration Rate

GIT----------Gastro Intestinal Tract

ICU----------Intensive Care Unit

HL----------Hodgkin's Lymphoma

KNH----------Kenyatta National Hospital

KS----------Kaposi sarcoma

NHL----------Non Hodgkin's Lymphoma

TLS---------- Tumour Lysis Syndrome

OPD---------- Out Patient Department

SPSS-10----------Statistical Package for Social Sciences Version 10

BRCA----------Breast Cancer

GIST----------Gastro Intestinal Stromal Tumour

CHOP----------Cyclophosphamide,Doxorubicin,Vincristine and Prednisone

ABVD----------Doxorubicin,Bleomycin,Vinblastine and Darcabazine

GTD----------Gestational trophoblastic disease(Choriocarcinoma)

HL----------Hodgkin's Lymphoma

ABSTRACT

BACKGROUND:

Tumour Lysis Syndrome (TLS) is a common occurrence following cancer treatment. It affects the treatment of both haematological and non-haematological tumours with a biochemical incidence of 42% among the acute leukemias and high grade lymphomas although only 3 - 6% manifest clinically.

Prophylactic measures such as hydration and adminstration of allopurinol are now widely used but published studies show persistence of the problem. This has been attributed to increasing use of more intensive and potent chemotherapeutic agents.

Development of TLS increases chemotherapy-related morbidity and if severe, mortality yet there are no local studies on TLS.

METHODOLOGY

STUDY DESIGN: This was a prospective cohort study conducted at the Kenyatta National Hospital (a tertiary and national referal center). Patients were recruited from oncology, medical and Gynaecology wards and also the haematology-Oncology, and radiotherapy clinics.

The study population consisted of patients with a confirmed tissue diagnosis of cancer receiving the first course of chemotherapy.

SCREENING AND RECRUITEMENT

Patients with a tissue diagnosis of cancer for whom chemotherapy had been prescribed were introduced to the study by use of the patient explanation form shown in appendix 1.

Those who met the inclusion criteria and signed the consent form were consecutively recruited into the study. Two milliliters of venous blood was withdrawn before starting chemotherapy and thereafter daily for four days.

Serum potassium, phosphate, calcium and uric acid were measured. Patients who developed TLS had repeat measurements on day 7 to check for resolution. Those who had not resolved had measurements repeated on day 15.

TLS was defined as a rise in serum potassium,phosphate and uric acid or decline in serum calcium by 25% occurring within four days of starting chemotherapy. A minimum of 2 out of these 4 biochemical changes were required for diagnosis of TLS.

RESULTS

A total number of 142 cancer patients were recruited. Out of these, 31 dropped out of the study thus leaving 111 patients for analysis. Incidence of TLS was found to be 37.83%(,95% C.I= 31.27-44.29).

Incidence of TLS in the haematological malignancies was 75.5%(95% C.I=67.64-83.37%) and in the non-haematological malignancies, it was 3.6%(95% C.I=-0.8-7.8%). Potassium and phosphate were the most consistent diagnostic parameters while only one patient had a rise in uric acid and no patient had a decline in calcium by 25% from baseline. Fifty percent of TLS cases developed on day 1 and 42.9% resolved in the second week.

CONCLUSIONS

The incidence of TLS at Kenyatta National Hospital from this study is 37.83%(95% C.I= 31.27-44.29).

Most of the TLS cases were diagnosed on the basis of increase in serum potassium and phosphate.

Uric acid levels did not appear to rise as would have been expected except in in one patient who received doxorubicin for abdominal rhabdomyosarcoma.

1. LITERATURE REVIEW

1.1 INTRODUCTION

Tumour lysis syndrome refers to a group of biochemical changes that occur following rapid death or cytolysis of malignant cells with release of intracellular components to the extracellular environment. The main biochemical changes involve increase in serum phosphate, potassium, and uric acid, and decline in serum calcium. In some of the patients,the biochemical changes can manifest clinically as renal, cardiac, muscle, and neuronal dysfunction. Cytolysis of tumour cells can be caused by chemotherapy, radiotherapy, or it can occur spontaneously (1).

There are two types of chemotherapy-related tumour lysis syndrome (TLS) as defined by Hande and Garrow in 1993 (1) :

Laboratory tumour lysis syndrome refers to a minimum of two of the following metabolic changes occurring within four days of initiating chemotherapy: a 25% increase in serum phosphate, potassium and uric acid, or a 25% decline in the serum calcium concentration. Clinical tumour lysis syndrome is defined as laboratory tumour lysis plus one of the following; renal failure, cardiac arrhythmias or sudden death (1).

In addition,high serum levels of lactate dehydrogenase (LDH) >1500 U/L, disseminated intravascular coagulation and fever may develop (2).Thus TLS may easily pass for infection or bone marrow suppression which are two of the most common complications of chemotherapy (3). Sometimes it can occur concurrently with bone marrow suppression and infection with fatal consequences (4).

In 2004, Cairo and Bishop suggested a modification of the Hande and Garrow definition to include patients whose serum potassium, phosphate and uric acid were above the upper limit of normal and calcium below the lower limit of normal. Using this definition increases the number of patients diagnosed with TLS (5).

1.2. IMPORTANCE OF TLS

TLS has been found to occur in 70% of leukemias and lymphomas although less than 6% manifest clinically(1). TLS is important because hyperuricaemia, hyperkalaemia,hyperphosphataemia and hypocalcaemia can cause renal failure, cardiac arrest, and neuronal dysfunction. Prevention and early detection are the most important and effective interventions in the management of TLS.

Hyperkalaemia

Hyperkalaemia is the most life threatening, occurring 6-72 hours after initiation of chemotherapy. It can cause tachycardia, muscle weakness, twitching, paraesthesia, paralysis, muscle cramps, and increased bowel sounds, nausea and vomiting, diarrhoea, lethargy ,metabolic acidosis and syncope (6).

Hyperphosphataemia and secondary hypocalcaemia

Hyperphosphataemia develops 24-48 hours after initiation of chemotherapy. Symptoms of hyperphosphataemia include azotaemia, oliguria, hypertension, and renal failure. Hypocalcaemia occurs secondary to hyperphosphataemia. Symptoms of hypocalcaemia include heart block, arrythmias, cardiac arrest, lethargy and mental status changes such as anxiety, depression, confusion hallucinations and a positive Chvostek's sign (7).

Hyperuricaemia

Hyperuricaemia is generally asymptomatic until uric acid levels exceed 10mg/dl and manifests as nausea, vomiting, diarrhoea, anorexia, fever, flank pain, metabolic acidosis, gout pruritus and acute renal failure (2).

Uric acid induced nephropathy exaggerates chemotoxicity of drugs undergoing renal excretion such as bleomycin,melphalan,6-mercaptopurine and azathioprine.This can prolong the duration of metabolic derangements resulting from sustained cytolysis (8).

Biochemical monitoring can help to detect TLS before it becomes clinically manifest. Clinically manifest TLS has a low incidence(3-6%). When it occurs, it constitutes an oncologic emergency. Without active intervention, it can be fatal or cause long-term disability like stroke, cardiac failure, and Chronic Renal Failure (CRF). Reliance on clinical manifestations to diagnose TLS has led to under reporting because about 94% of patients with TLS are asymptomatic. These mild to moderate cases meet the diagnostic criteria of TLS and can interrupt treatment but often go unreported because they are subclinical (7).

Biochemical monitoring for TLS can also help in early identification of treatment responsive tumours. Initial chemotherapy that is not associated with change in serum,phosphate,potassium, uric acid, and calcium may be an indicator of primary tumour resistance to treatment (9).

The combination of prevention and early detection of TLS has reduced the mortality rate of acute hyperuricaemic nephropathy from 50% in the last 30 years to almost zero in North America (7).

1.3. PATHOGENESIS OF TLS

TLS occurs as a result of successful oncolytic chemotherapy (tumor overkill syndrome) (10). Rapid cytolysis releases intracellular nuclear and cytoplasmic contents into the circulation (11).

Chemotherapy causes cytolysis which releases intracellular ions and metabolic products into the blood. Hyperuricemia, hyperphosphataemia,and hyperkalemia are primarily derived from cytolysis and release of intracellular contents. Hypocalcemia has been ascribed to extraskeletal calcium phosphate deposition. In addition, phosphate retention alters the hydroxylation of vitamin D_3 in the renal tubular cells, inhibiting conversion of 25 – hydroxycholecalciferol to the active metabolite 1, 25- dihydroxycholecalciferol. This leads to inability to absorb calcium from the gastrointestinal tract or mobilize it from bone.

Although transient hyperparathyroidism occurs, it is not sufficient to normalise the hypocalcaemia(12).

Hyperkalaemia is often the earliest laboratory manifestation.While hyperkalaemia is a direct result of rapid cell lysis, hyperphosphataemia results from both rapid cell lysis and decreased reutilization of phosphate by the malignant cells (11).

Hyperphosphataemia is more common in acute lymphoblastic leukemia because lymphoblasts contain four times the amount of phosphate in mature lymphocytes. Both hyperkalaemia and hyperphosphataemia are exacerbated by metabolic acidosis which impairs their cellular uptake (12).

Hypocalcaemia occurs secondary to acute hyperphosphataemia with subsequent precipitation of calcium phosphate in soft tissues (13).

Hyperuricaemia

Nucleic acid purines which are also released by cell breakdown are ultimately metabolized to uric acid by hepatic xanthine oxidase. Uric acid accumulates due to overwhelmed renal excretion and saturation of endogenous uricase which usually converts uric acid to the more soluble allantoins(8).

Hyperuricaemia causes precipitation of uric acid crystals in the distal tubules,collecting ducts, and ureters causing obstructive uropathy (14).

Metabolic acidosis is due to the liberation of large amounts of endogenous intracellular acids. This depletes serum bicarbonate resulting in a high anion gap acidosis. Acidosis impairs intracellular potassium uptake, decreases uric acid solubility and promotes extra cellular shift of phosphates (7).

ARF is mainly due to obstruction of renal tubules by crystallized uric acid, calcium phosphate,and hypoxanthine. The crystallization of uric acid is 13 times faster at urine PH <7.0. This is the basis for alkalinization of urine (11).

The in vivo ion solubility product of calcium x phosphate is about 4.6 mmol/ l to 5.6mmol/l , above this, calcium phosphate precipitates in the tissues and tubules (3).

Alkali promotes solubilization of uric acid crystals but at urine ph>7.5,increases crystallization of calcium phosphate,xanthine,and hypoxanthine (15).

The rate of cytolysis decreases after 48-72 hours unless the same treatment is repeated or a new and more potent drug is given to the patient. The metabolic disturbance resulting from TLS usually lasts for 6-7 days because of the finite period of cell lysis (10,16).

1.4. DETERMINANTS OF TLS

The factors that determine the occurrence of TLS can be divided into three groups; Tumour factors, Patient factors, and treatment factors.

Tumour factors

TLS is most common in patients receiving treatment for haematological malignancies. In the high-grade lymphomas,incidence rates of 70% have been reported (17). It is however well established that any tumour that is highly responsive to therapeutic agents can give rise to TLS. This has lead to the suggestion that the development of TLS can be used as a marker of tumour response to treatment (11).

Kevin Lee (18) has classified tumours according to risk of TLS as follows:

Highest risk

- Aggressive lymphomas
- Acute leukaemias

Moderate risk

- Low grade lymphoma
- Multiple myeloma
- Breast cancer
- Small cell lung cancer
- Germ cell tumours

Lowest risk

- Medulloblastoma
- Gastrointestinal tract adenocarcinomas

Bulky tumours (greater than 8 centimeters in diameter) and tumours with a high proliferative rate(more than 10 mitoses per 10 high power fields) are also associated with increased incidence of TLS (10). Chemosensitivity of tumours also predicts TLS occurrence with higher rates being reported in the most chemosensitive tumours such as high-grade lymphomas,acute lymphoblastic leukaemia and germ cell tumours (17).

Treatment factors

Most chemotherapeutic drugs including interferons, interlukins, and intrathecal methotraxate have been reported to cause TLS (7). High dosage per meter square of body surface area and combination of potent drugs predisposes patients to TLS through increased cytolysis.(3)

Although most of the cases occur during initiation of therapy, TLS can also occur with repeat cycles of chemotherapy especially when rapidly growing tumours are treated with long inter-cycle interval protocols (9).

As new and more specifically cell-directed cancer treatments evolve, it is possible that the incidence of the condition will increase (7).

Patient factors

Patients with renal impairment before initiating chemotherapy are predisposed to TLS due to diminished excretory function. Dehydration also predisposes patients to TLS. Hyperphosphataemia predicts TLS because it may be a manifestation of rapidly proliferating and dying tumour cells as occurs in acute lymphoblastic leukaemia while hypophosphataemia may be due to increased cellular uptake by rapidly proliferating tumour cells(12).

1.5. STUDIES ON TLS

To detect TLS, plasma levels of phosphate, potassium, uric acid, and calcium are measured daily for four days after initiation of chemotherapy. If the values of uric acid, phosphate,and potassium increase by 25%, and calcium drops by 25% , TLS is in progress (1,5). All the studies quoted in this literature review were conducted in North America and Europe in a predominantly Caucasian population. No local or regional studies were found in published literature.

Incidence of TLS

Hande and Garrow reported an incidence of laboratory TLS of 42% in 102 patients, at Vanderbilt University in North America (1).

Cohen et al studied 37 patients out of whom 14 (38%) developed azotaemia,most of the study subjects were receiving treatment for non-Hodgkin's lymphoma (19).

In a retrospective study, Arseneau et al reported 25% incidence of ARF in 37 patients receiving treatment for Burkitt's lymphoma. (20).

De Conti et al reported chemotherapy-related hyperuricaemia as the most frequent cause of ARF in leukemia patients, incidence was 50% (21).

Haas et al reported a 14% incidence of azotaemia in patients with various haematological tumours (22).

In a more recent review by Koyamangalath and colleagues in patients with intermediate-grade or high-grade non-Hodgkin's lymphomas (NHL), the incidence of biochemically and clinically manifest TLS was estimated at 42% and 6% respectively. In children with acute leukaemia TLS occurs in 70% but only 3% are symptomatic. The authors project that the incidence will continue to increase as high dose regimens and more cytotoxic agents become available (7).

Biochemical findings in TLS

In a prospective study by Carl et al at the University of Minnesota, ARF occurred at a mean uric acid plasma level of 1.19mmol/l, range 0.68mmol/l to 2.11mmol/l. Hyperphosphataemia was reported in 1 out of the 16 patients (23) ,lower than 38% in Cohen's study (19). The hyperphosphataemia was significantly correlated with the serum creatinine($r=0.895$, p value < 0.001) (23).

Hyperphosphataemia with ARF may occur in the absence of hyperuricaemia ,and has been found to be more common than hyperkalaemia and hypocalcaemia (24).

Hyperkalaemia is highly variable being reported as most common by Cohen (19) and Arseneau (20), but least common by Jaime (12) and Ettinger (24).

In Cohen's study,hyperkalaemia occurred earliest in four patients within 12 hours of initiating therapy. He postulated that acute "hyperkalaemia resulting from chemotherapy was probably responsible for sudden deaths of some of these patients "(19).

Hypocalcaemia is the least common, (10%) usually secondary to hyperphosphataemia and persists longer than hyperuricaemia (13).

Biochemical outcomes in TLS

The prognosis of TLS is good if detected early (22). It has been reported that the elderly have a more severe disease(7),but most studies have found virtually 100% recovery even in patients who required haemodialysis (19). In the study by Carl et al,the mean age was 27.7 years, range 6-73 years. Fifteen out of the sixteen study subjects had normalized biochemical parameters after 7 days (23).

Haas et al reported that most cases of ARF reversed after 2 sessions of haemodialysis (22).

Although patients with pre-treatment deranged renal function and dehydration are predisposed to TLS, the prognosis improves if it is detected early and treatment given (24).

Predictors of TLS

Patients with haematological malignancies have the highest incidence (70%) while it is rare in tumours arising from the gastro intestinal tract (18).

Multiple myeloma (MM), a clonal neoplasm affecting terminally differentiated B lymphocytes, has been traditionally viewed as a hypoproliferative malignancy, at least untill the terminal phase of the disease which is characterized by increased plasmablasts, a high growth fraction and frequent extramedullary involvement.

In a retrospective analysis of 800 patients treated with intermediate and high dose chemotherapy, nine patients developed TLS . The mean values of post-chemotherapy potassium, phosphate and uric acid were higher than those reported by both Cohen et al (19) and Tsokos et al (25) in their lymphoma series . All patients had extensive bone marrow plasmacytosis. Hyperproliferative disease, as measured by plasma cell labeling index, and immature morphology as measured by the presence of plasmablasts, were present in the majority of the patients. Seven out of eight patients had unfavourable cytogenetic abnormalities. All these features of increased proliferation predispose patients with multiple myeloma to development of TLS (25).

TLS is known to occur in chronic lymphocytic leukaemia (CLL) and sometimes it can be fatal (26,27).

In chronic leukemias, TLS presents with fever and could easily pass for infection with fatal consequences (26).

TLS has been documented to occur in breast cancer (28,29). The risk factors for TLS development in breast cancer include rapidly growing adenocarcinoma, markedly elevated lactate dehydrogenase and deranged blood urea nitrogen(30). Patients receiving 5-fluorouracil, doxorubicin and cyclophosphamide are at much higher risk. TLS usually develops within 72 hours and can be fatal (31). It has been suggested that such patients should be identified and put on prophylactic allopurinol (17,30) . It occurs in both males and females (32).

A total of 45 non-haematolgical cancer patients receiving treatment were reviewed by Baecksgaard et al (33) and found to have TLS. Most of these patients had metastatic disease Similar results were reported by Drakos et al (30). Kattan et al (32) reviewed retrospectively 46 non haematologic tumours treated with cisplatin based regimes. All the patients received six liters of fluids 24 hours before induction and were monitored for seven days after starting chemotherapy. None of the patients developed TLS. They concluded that TLS is rare in solid tumours and special prophylactic therapy is unnecessary.

Gregory et al(33) studied the risk factors in 25 TLS positive patients with solid tumours. Five had breast cancer. The common risk factors reported included pretreatment renal insufficiency, elevated LDH and hyperuricaemia. Acute renal insufficiency and hyperuricaemia were identified in nearly all patients while hyperkalaemia, hyperphosphataemia, hypocalcaemia and increased serum LDH were reported in over 75% of patients. Nine of the twenty five patients died during the acute episode of TLS.

Patients with rapidly growing ovarian cancer have also been reported to develop TLS although these cases were mild and treated conservatively (34).

All patients with choriocarcinoma are at high risk of developing TLS and those with metastatic disease are at the highest risk (35). When the lungs are involved, then hypoxia with respiratory arrest can follow if mechanical ventilation is delayed (36).

Bulky tumours with a high mitotic rate are also associated with TLS as reported by Boccia et al who found that tumours greater than 8 centimeters in diameter and having more than 10 mitoses per 10 high power fields predict occurrence of TLS (9).

The commonest risk factors as described by Cohen et al are: a large tumour burden, serum LDH above 1500 IU, extensive bone marrow involvement, high tumour sensitivity to chemotherapeutic agents, young male patients (often <25 years) , and concentrated acidic urine (19).

Most chemotherapeutic agents including interferon and tamoxifen can cause TLS (38,39). Change to a new drug in the course of treatment can also precipitate TLS especially if the new drug is more potent than the initial therapy (39). Intrathecal methotraxate can also cause TLS (40).

Dehydration and impaired renal function before initiation of chemotherapy have been reported as risk factors for TLS development (15).

Both hyperphosphataemia and hypophosphataemia can predict TLS. This is because hyperphosphataemia may be due to increased cytolysis while hypophosphataemia may be due to increased tumour uptake by rapidly proliferating cells (12).

The performance status of patients according to algorithms such as the one developed by Karnofsky or by the Eastern Cooperative Oncology Group (ECOG) predict the overall outcome of therapy. It is now recommended that if there is curative potential,even poor performance patients may be treated although their prognosis is inferior compared to patients with good performance status. TLS can contribute to the poor performance status during chemotherapy (39).

1.6.PREVENTION AND TREATMENT

The current management of TLS includes hydration, administration of sodium bicarbonate to treat metabolic acidosis, diuretics when indicated and the reduction of uric acid levels using allopurinol or urate oxidase (uricase) (5).

If Acute Renal Failure (ARF) occurs, intensive care with haemodialysis may be required. Peritoneal dialysis can also be used but has been found to be 10-20 times less efficient for uric acid clearance compared to haemodialysis (3).

Although prophylactic allopurinol and fluids are preventive, TLS occurs in well hydrated patients receiving allopurinol (1).

Allopurinol(4-Hydroxypyrazolo-3,4-d pyrimidine) and its principal metabolite oxypurinol inhibit xanthine oxidase resulting in increased urine xanthine and hypoxanthine which is less soluble than uric acid. Xanthine crystalluria and calculi have been reported to cause renal dysfunction especially in patients with Lesch- Nyhan syndrome (39). Other limitations of allopurinol include inability to decrease uric acid already formed,and the need to adminster it continuously for two weeks before a steady state is achieved (42,43).

Hydration is limited in patients with compromised renal or cardiac function because of the increased risk of developing fluid overload. Inability to monitor central venous pressure may also contribute to inadequate fluid administration and subsequent development of TLS. Hydration can also be complicated by the anti-diuretic effects of cyclophosphamide and vincristine (42). 3,000ml/m^2 per day of 5%dextrose in 0.2% normal saline have been recommended as adequate hydration (28,37).

Alkalinization of urine is limited because it enhances nephrocalcinosis from calcium phosphate crystals, which crystallizes at alkaline PH unlike uric acid which crystallizes at acid PH (12).

Exogenous calcitriol supplementation can correct hypocalcaemia but this enhances metastatic calcification (13).

Haemodialysis may be required if there is no response to parenteral fluids ,sodium bicarbonate, and allopurinol (44).

Current, prophylaxis and therapy is focused on use of pegylated recombinant uricase 0.20mg/kg/day. This has been shown to reduce uric acid to undetectable levels within four hours of administration followed by reversal of ARF(8). However,uricase is not widely available. Recognition of risk and prevention are the most important steps in the management of TLS (5).

2 STUDY JUSTIFICATION

TLS commonly occurs following chemotherapy even when patients are well prepared before initiating treatment. It can interrupt therapeutic protocols, increase morbidity, adversely affects clinical outcome and in severe cases, can cause death.

In Africa in general and Kenya in particular, studies on TLS are lacking. This hospital-based observational prospective study aimed to establish local incidence and associated factors of TLS and hence bridge the existing knowledge gap.

Identification of possible predictors of TLS was felt could help to prevent its occurrence since they will be corrected prior to initiating therapy in future patients.

By determining the biochemical derangements in TLS patients, a rational management protocol can be developed thus saving scarce laboratory resources.

3 OBJECTIVES

3.1 Broad objective

To estimate the magnitude of Tumour Lysis Syndrome at KNH,identify its pattern of presentation and predictors, and determine the biochemical outcome of affected patients.

3.2 Specific objectives

1. Determine plasma uric acid,phosphate,potassium, and calcium changes in patients receiving chemotherapy from day 1 to 4,then 7 and 15.
2. Determine the incidence of biochemically manifest Tumour Lysis Syndrome at KNH.
3. Determine the incidence of Tumour Lysis Syndrome in haematological and non- haematological malignancies.
4. Determine the incidence of Tumour Lysis Syndrome in patients with Karnofsky Perfomance Score below 70.
5. Determine plasma uric acid,potassium,phosphate, and calcium 7 days after development of tumour lysis syndrome.

4.0 . METHODOLOGY

4.1. **Study design.** This was a prospective cohort study. It was conducted at the Kenyatta National Hospital (a tertiary national referral centre) in Oncology, Medical, and Gynaecology wards and also in haematology- Oncology, and Radiotherapy clinics.

4.3 . STUDY POPULATION AND ENTRY CRITERIA

The study population was patients at KNH with a documented tissue diagnosis of cancer receiving first course of chemotherapy, with minimum glomerular filtration rate (GFR) of 90mls/min/1.73m2.

4.4 . INCLUSION CRITERIA

The study included patients aged 13 years and above with documented tissue diagnosis of cancer and receiving the first course of chemotherapy. The patient or guardian had to sign the consent form voluntarily after receiving the necessary explanation.

4.5 . EXCLUSION CRITERIA

The study excluded patients receiving uricosuric agents for indications other than TLS and post-renal transplant patients. It also excluded dehydrated patients and those unwilling to come back to the hospital for four consecutive days.

4.6. SCREENING AND RECRUITMENT

The principal Investigator visited the study sites according to a specified time table (table 1).

DAY	AM	PM
MONDAY	Haematology/Oncology clinic	Wards
TUESDAY	Oncology ward (GFD)	Wards
WEDNESDAY	Radiotherapy clinic	Wards
THURSDAY	Radiotherapy clinic	Wards
FRIDAY		Wards
SATURDAY		Wards

TABLE 1

Patients for whom chemotherapy had been prescribed by the primary care clinician were identified by reading through their files and introduced to the study. Those who consented had their personal details taken as per the proforma form in appendix 7. For patients who declined to consent,only age,gender and tumour type were recorded. Patient records were adequate in meeting the study objectives.

The decision to start chemotherapy was entirely by the primary care clinician as per the protocal of K.N.H. The investigators did not influence the decision on who gets and who does not get therapy. The patients who received chemotherapy were consecutively recruited into the study. At the end of recruitment, study subjects reflected the usual pattern of patients receiving chemotherapy at KNH. Breast cancer is the commonest followed by haematological malignancies.

The glomerular filtration rate (GFR) was calculated using the Cockroft-Gault Formula:

Creatinine Clearence in mLs/min =

$$\frac{\text{(140-age in years) xbody weight in kg}}{\text{plasma creatinine in mmol/lx0.81}} \qquad (\text{Females x } 0.85)$$

4.7. SAMPLE SIZE The sample size was calculated according to this formula (45).

$$n = \frac{(Z1-\alpha/2\,\lambda o + Z1-\beta\,\lambda a)^2}{(\lambda o - \lambda a)^2}$$

$$= \frac{(1.96 \times 0.42 + 0.842 \times 0.55)^2}{(0.42 - 0.55)^2} = 97$$

+ 10 anticipated fall out = 107

where

n = sample size

Z = standard normal deviation with 80% power

α = significance level = 0.05.

λo = hypothesised incidence(from other studies)=42%

λa = estimated actual incidence =55 %

$Z1-\beta$ =0.842 with β =20%

4.8. FOLLOW UP

Patients were reviewed daily from day 0 to day 4. On each review, blood samples were collected as explained under laboratory methods. Those developing laboratory TLS were reviewed on day 7 to check for biochemical resolution. Those who had not resolved by day 7 were again reviewed on day 15.To avoid a high rate of drop out, the principal investigator and patients used telephone contacts where available to remind each other when appointments were due.

5.0. CLINICAL METHODS

The principal investigator took history to document biodata, and functional status and examined patients to document weight, height, hydration status and overall clinical state. The Karnofsky Perfomance Scale was used to assess functional status. It is an internationally validated instrument for this purpose.

All recruited patients underwent pretreatment evaluation for plasma uric acid, urea, creatinine and potassium on day 0, which provided baseline information. After chemotherapy was initiated, the tests were done at 24 hour intervals for four days.

Patients who developed laboratory TLS had tests repeated after 7 days to check for biochemical resolution. If there was no resolution by the 7th day, further testing was carried out on day 15.

6.0. LABORATORY METHODS

6.1. SPECIMEN COLLECTION

Two milliliters of venous blood was collected in a clean, plain bottle using aseptic technique.

Each specimen was analysed at KNH Clinical Chemistry Laboratory .

Haemolysed samples were discarded and another specimen collected.

Results were communicated to the patient and primary care clinician.

6.2. BIOCHEMICAL ASSAYS

Uric acid, phosphates, Calcium, BUN, and Creatinine were analyzed by the Olympus AU400 automated clinical chemistry analyser based on the methods described by Trinder and Fossati (46).

Calcium was corrected for serum albumin using the formula:

Corrected calcium(mmol/l) =

measured calcium(mmol/l) +0.02(40-albumin(g/l)) (47).

6.3. QUALITY CONTROL

The procedures of specimen collection and preparation were followed strictly to minimise preanalytical sources of error. Before analysis, all the assays were calibrated according to the manufacturer's specifications. Three levels of control (high,medium and low) were used to validate the calibration.The results were only accepted if the controls were within the accepted limits (48).

6.4. CASE DEFINITION OF TLS

This study adapted the Hande and Garrow definition of laboratory tumour lysis syndrome because it has been widely used in other published studies (1,5,10).
A case of TLS was defined as a patient who met any two or more of the following criteria within four days of receiving chemotherapy.

1. Increase in serum uric acid, phosphate,and potassium by at least 25% from baseline.
2. Decline in serum calcium by at least 25% from baseline.

6.5. DURATION OF STUDY

This study was conducted between November 2004 to April 2005.

7.0. RESULTS

A total number of 366 patient files with tissue diagnosis of cancer were reviewed between November 2004 and April 2005 (see flow chart in appendix 10.7). Two hundred and eight patients prescribed chemotherapy were identified. One hundred and eighty seven met the study entry criteria of normal renal function.

Forty five patients were excluded after they withdrew consent because they were unwilling to come back to the hospital for four consecutive days.

The baseline characteristics of excluded patients have been summarised in figure 1,2b, and table2.

Thirty one patients dropped out of the study because of missing some drugs or loss of follow up from the clinic . The distribution of tumours in these patients is shown in table 3. One hundred and eleven patients completed the study and were analysed. Data from all the 187 patients show that the included and excluded groups had similar baseline characteristics.

Baseline characteristics of the 111 study subjects and 45 exclusions are presented followed by the 42 patients who developed TLS.

7.1. BASELINE CHARACTERISTICS

7.1.1. AGE DISTRIBUTION OF THE INCLUDED AND EXCLUDED SUBJECTS:

The age range of 111 study subjects was 14 to 75 years, mean age 40.5 years (figure 1).

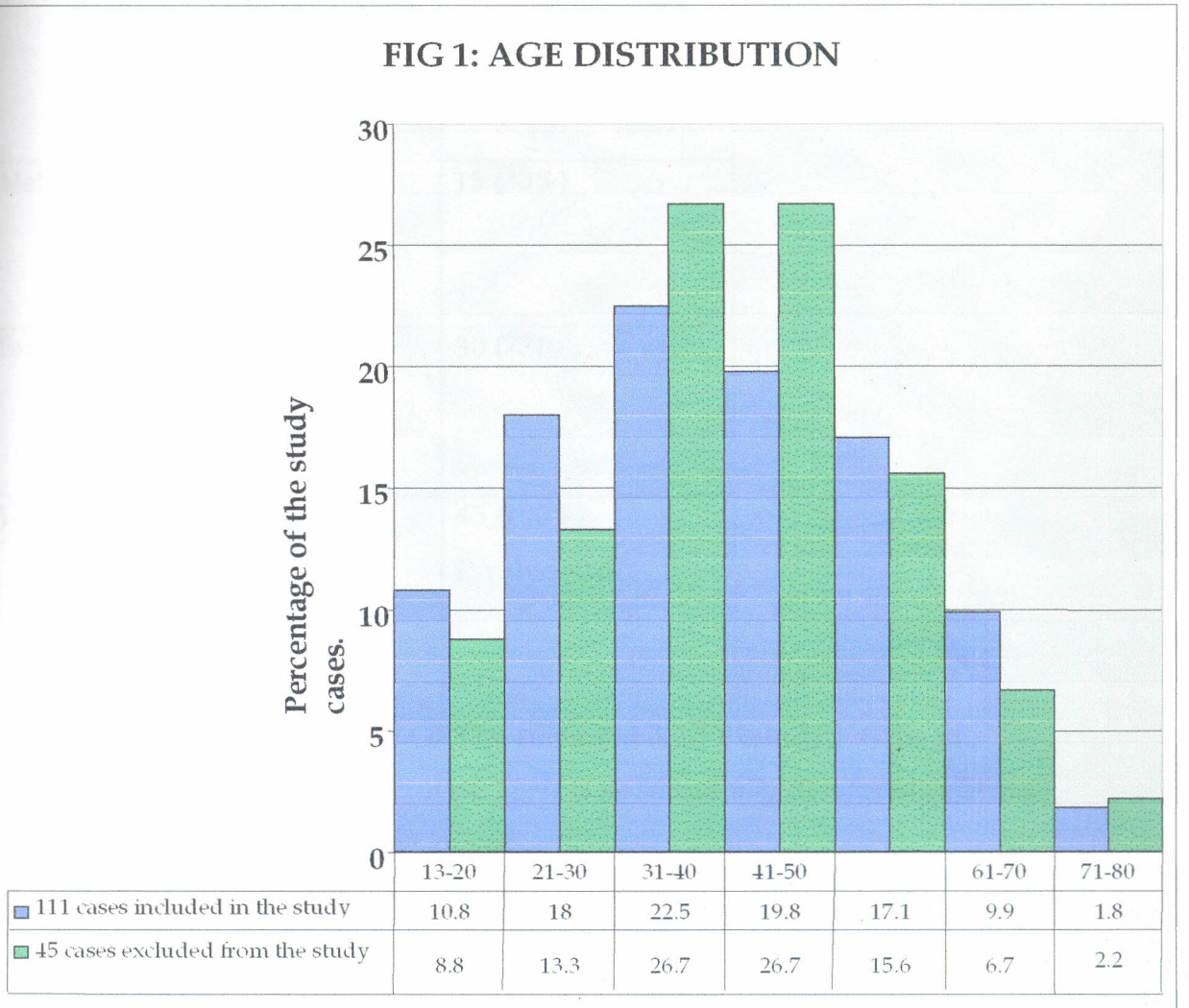


FIG 1: Age Distribution Of The Included And Excluded Subjects

7.1.2 MALE TO FEMALE RATIO OF INCLUDED AND EXCLUDED PATIENTS.

More females than males were recruited into the study with a male: female ratio of 0.6:1. A similar ratio was seen in the excluded group (table 2).

	Included	Excluded
Males	41 (37%)	15 (33%)
Females	70 (63%)	30 (77)
Total	111 (100)	45 (100%) P value=0.67

Table 2: Gender Distribution Of The Included And Excluded Groups.

More females than males were recruited. There is no statistically significant difference between the included and excluded groups.

7.1.3. DISTRIBUTION OF TUMOURS IN THE INCLUDED AND EXCLUDED PATIENTS.

Majority (40.5%) of the 111 included cases had breast cancer (BRCA) followed by 16.2% with non -Hodgkin's Lymphoma(NHL). The third commonest type of neoplasm was chronic leukaemias(15.3%). The same pattern was seen in the 45 excluded patients where breast cancer comprised 42.2% followed by NHL with 15.6% and chronic leukaemias at 13.4%.Comparison of the 2 groups shows that they were similar.P value = 0.53 (figure 2a and 2b).

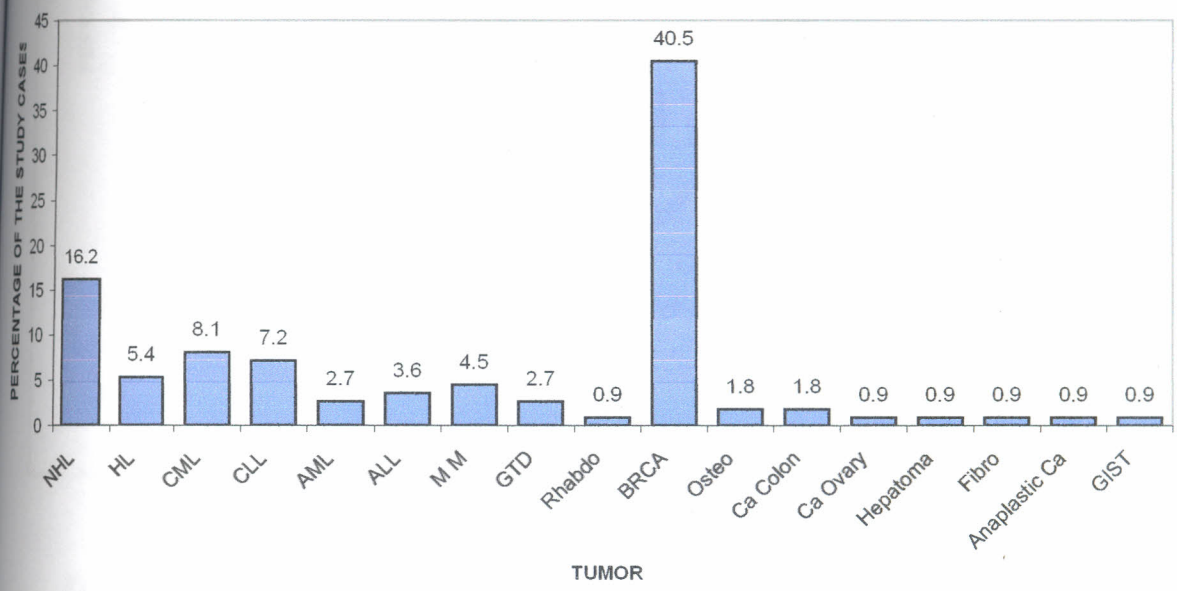


FIG2a: Tumour Distribution On The 111 Study Subjects.

Key.BRCA=Breast cancer,MM=Multiple myeloma, GIST=Gastro- intestinal stromal tumours Rhabdo=Rhabdomyosarcoma,Osteo=Osteogenic sarcoma,Fibro=Fibrosarcoma , GTD=Choriocarcinoma..HL=Hodgkin's lymphoma. CML= Chronic myeloid leukaemia.CLL= Chronic lymphocytic leukaemia.ALL=Acute lymphocytic leukaemia

Figure 2b shows the tumour distribution in the 45 patients who were excluded from the study. Breast cancer was still the most common followed by NHL.

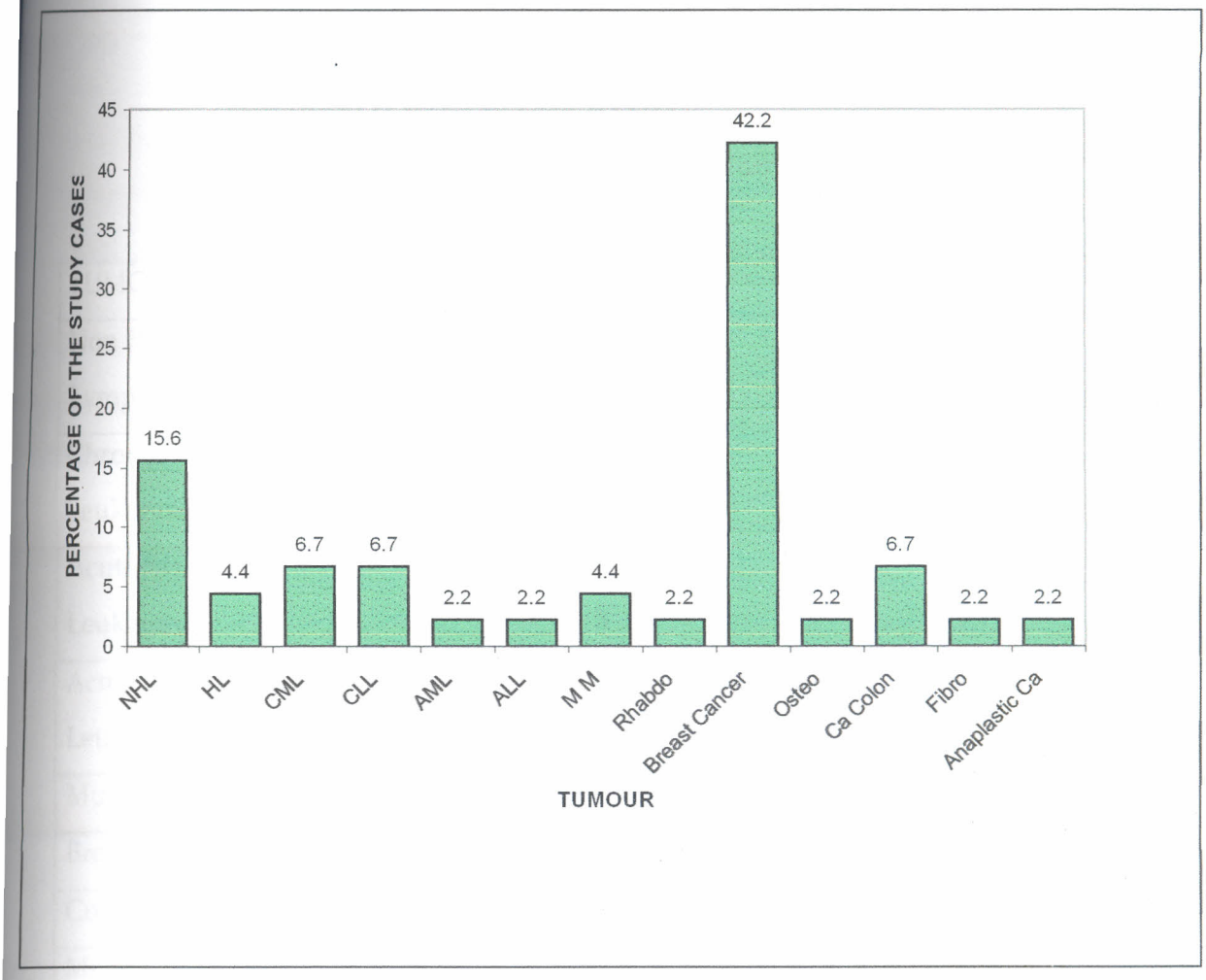


FIG 2b: Tumour Distribution Of 45 Excluded Patients

Key.MM=Multiple myeloma, GTD=Choriocarcinoma, Fibro=Fibrosarcoma Rhabdo=Rhabdomyosarcoma, Osteo=Osteogenic sarcoma, , GIST=Gastro intestinal Stromal Tumours. Anaplastic ca = metastases from undetermined sites. NHL=Non-Hodgkin's Lymphoma.CML=Chronic Myeloid Leukaemi.,AML=Acute Myeoid Leukaemia.ALL=Acute Lymphoblastic Leukaemia. Ca colon= Cancer of the colon.

7.1.3.b. TUMOUR DISTRIBUTION IN PATIENTS WHO DROPPED OUT OF THE STUDY

Breast cancer was the most common tumour in the 31 patients who dropped out of the study (table 3).

TUMOUR	NUMBER	%
Non Hodgkin's Lymphoma	10	32.3
Chronic Myeloid Leukaemia	2	6.5
Acute Myeloid Leukaemia	3	9.7
Acute Lymphoblastic Leukaemia	2	6.5
Multiple Myeloma	1	3.2
Breast cancer	11	35.5
Colon cancer	1	3.2
Melanoma	1	3.2
TOTAL	31	100

Table 3: Tumour Distribution Of 31 Patients Who Dropped Out Of The Study.

7.1.4. TUMOUR STAGE DISTRIBUTION

Most of the patients had advanced stage disease(III and IV). Only one patient with breast cancer had stage 1 disease.The percentage of patients with advanced stage disease was as follows; breast cancer 78% , non-Hodgkin's lymphoma 83%,chronic lymphocytic leukaemia 100% and Hodgkin's lymphoma 100%(table 4).

TUMOUR	Number	STAGE
Breast cancer	1	I
	9	II
	17	III
	18	IV
Non-Hodgkin's lymphoma	3	II
	7	III
	8	IV
Chronic lymphocytic Leukaemia	8	IV
Hodgkin's lymphoma	2	III
	4	IV
Others	13	IV
No staging (AML,ALL,MM)	21	------
Total	111	--------

Table 4 : Tumour Stage Of The 111 Study Subjects

Key.MM;Multiple myeloma.AMLand ALL;Acute leukaemias.

Others:Gestational trophoblastic disease ,Rhabdomyosarcoma ,Osteogenic sarcoma,Coloncancer,Ovarian cancer,Hepatoma,Fibrosarcoma

Metastases from unknown site and Gastrointestinal stromal tumour.

7.1.5. BASELINE ELECTROLYTE LEVELS

The baseline electrolyte levels for 142 patients recruited in the study were within the normal laboratory reference range for individual electrolytes(figure 3).The median value was used to summarise electrolyte changes because it is the best measure of central tendency when describing blood chemistry.

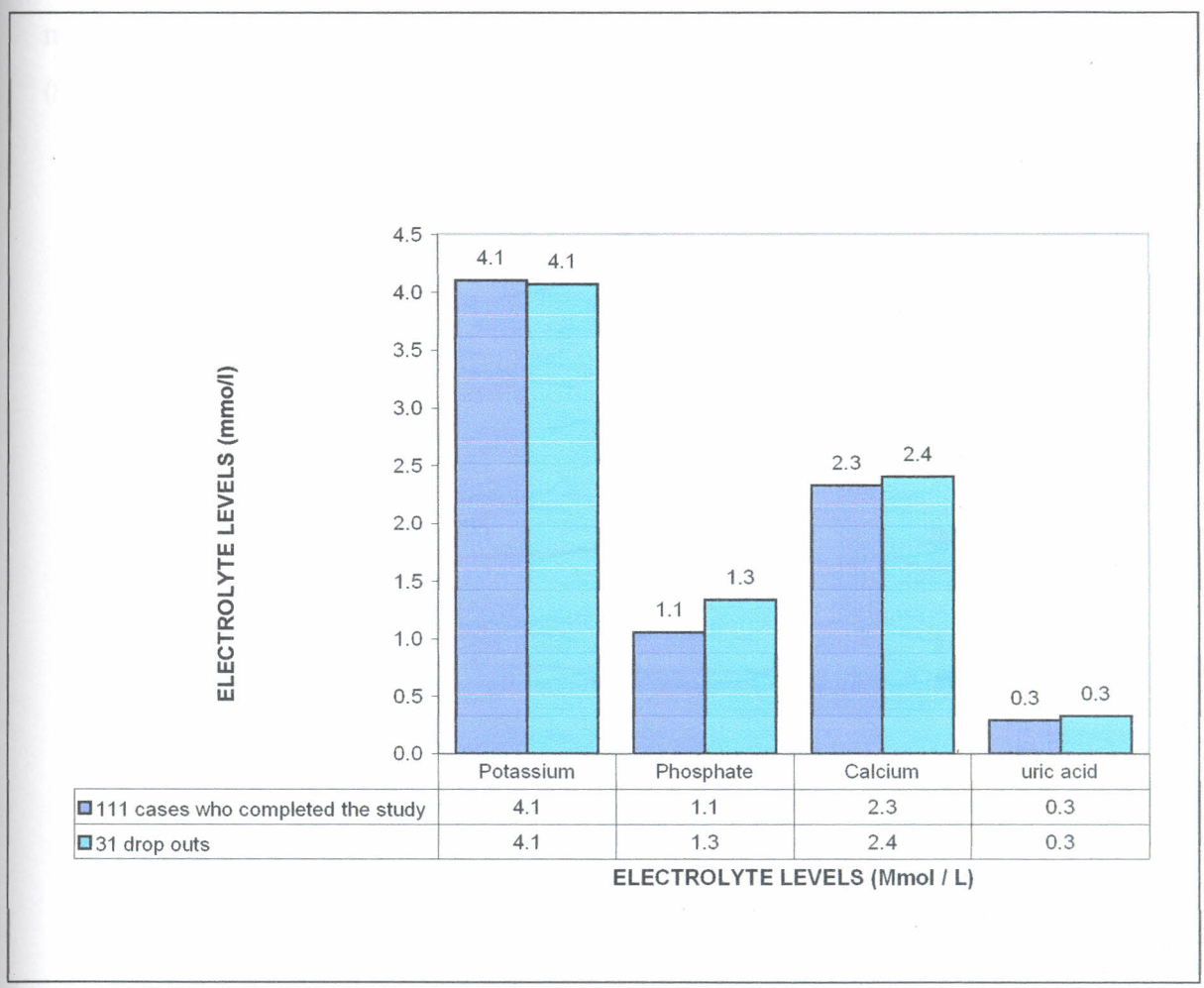
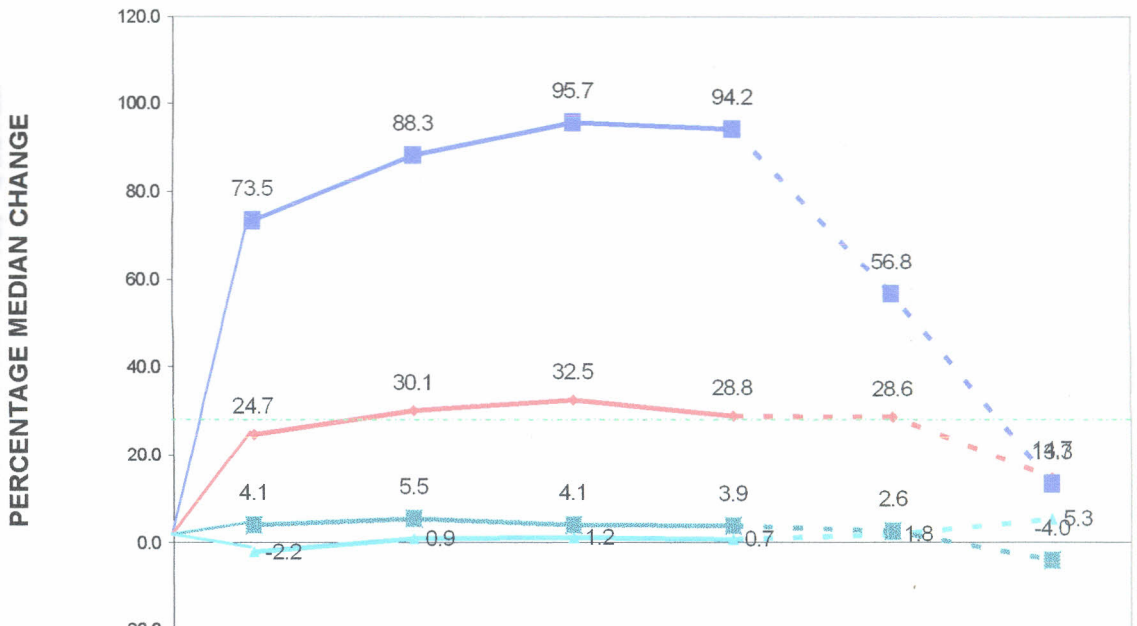


Figure 3: Baseline Serum Electrolytes For All The 142 Patients Recruited In The Study.

7.2. PERCENTAGE MEDIAN ELECTROLYTE CHANGES IN THE STUDY SUBJECTS

On day 1, there was a median increase in serum potassium of 24.7% while phosphates increased by 73.5%. The increase in uric acid was 4.1% while calcium declined by 2.2%. The highest increase was seen on day 3 when phosphates increased by 95.7% and potassium increased by 32.5%.Increases in serum calcium and uric acid were negligible at 1.2% and 4.1% respectively. Therefore on the basis of percentage change in electrolytes, only potassium and phosphate met the diagnostic criteria for TLS of increase by at least 25% from baseline (figure 4).



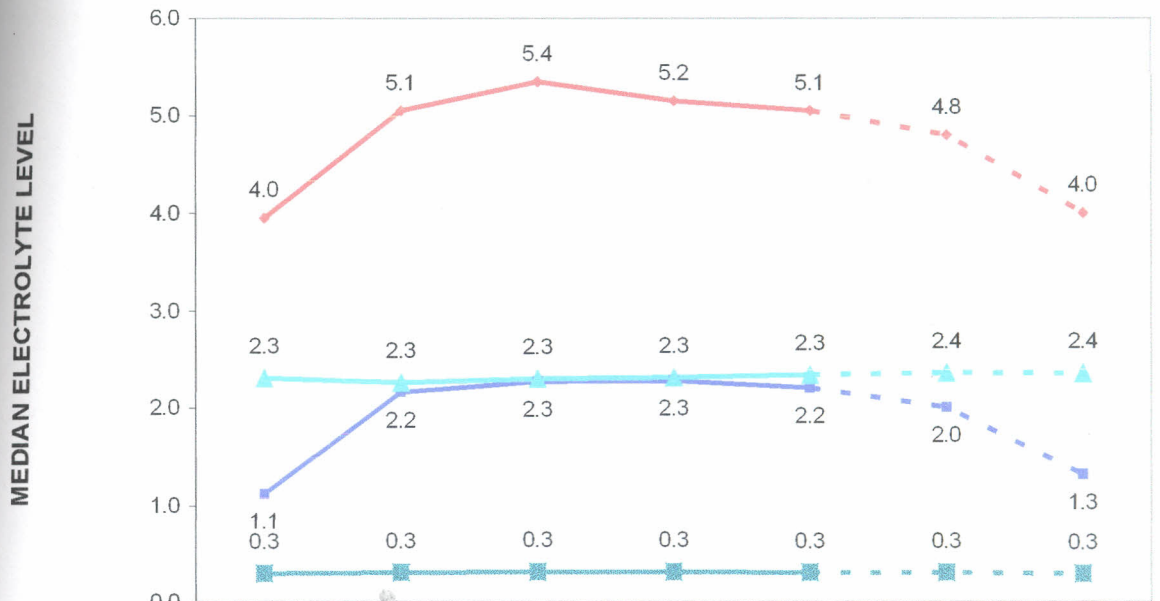
	Day 1	Day 2	Day3	Day 4	Day 7	Day 15
Potassium	24.7	30.1	32.5	28.8	28.6	14.7
Phosphate	73.5	88.3	95.7	94.2	56.8	13.3
Calcium	-2.2	0.9	1.2	0.7	1.8	5.3
uric acid	4.1	5.5	4.1	3.9	2.6	-4.0

Figure 4: Percentage Changes In Serum Electrolytes.

The dotted green horizontal line indicates the 25% cutoff point.Only potassium and phosphates cross this line on days 1,2,7 and 15.

7.2.1 MEDIAN ELECTROLYTE CHANGES (in mmol/l)

On the first day after adminstration of chemotherapy,serum phosphates increased from 1.1mmol/l to 2.2 mmol/l while serum potassium increased from 4.0 mmol/l to 5.1mmol/l The highest median values were seen on day 2 and 3 when phosphate was 2.3mmol/l and potassium was 5.4mmol/l.The median value for uric acid was 0.3mmol/l from day 1 to 15 while calcium was 2.3mmol/l from day 0 to day 4,then 2.4mmol/l on day 7 and 15(figure 5).

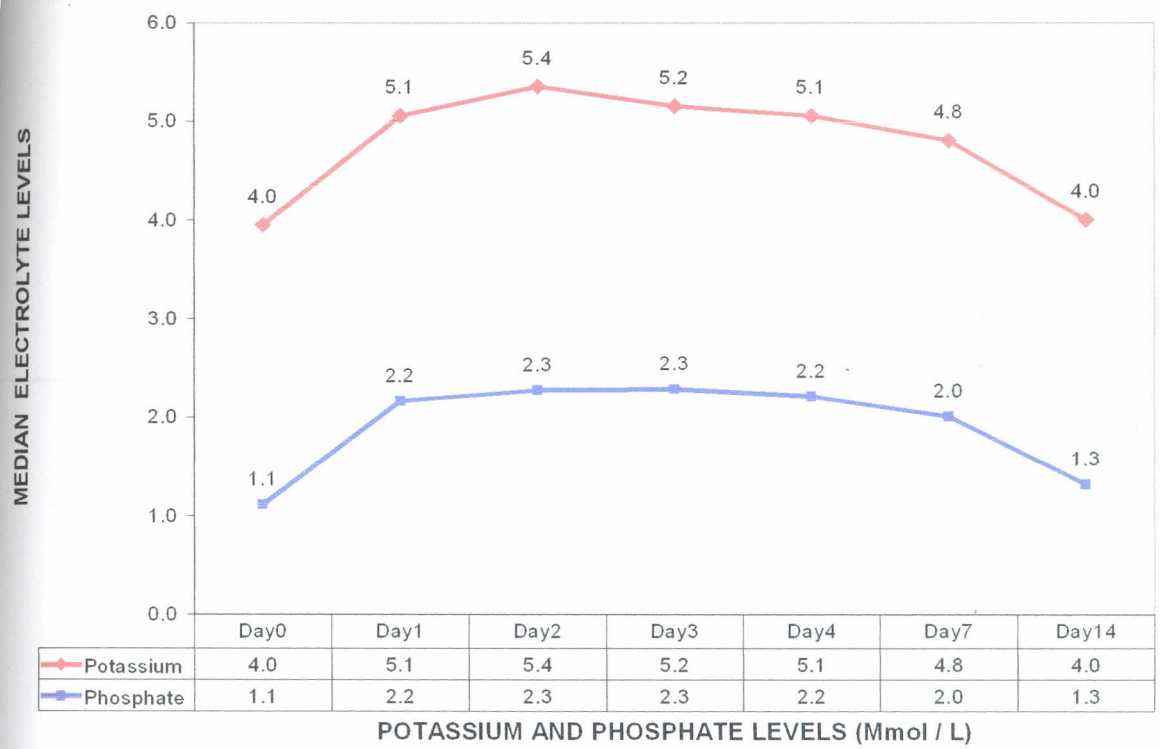


	Day0	Day 1	Day 2	Day3	Day 4	Day 7	Day 15
Potassium	4.0	5.1	5.4	5.2	5.1	4.8	4.0
Phosphate	1.1	2.2	2.3	2.3	2.2	2.0	1.3
Calcium	2.3	2.3	2.3	2.3	2.3	2.4	2.4
uric acid	0.3	0.3	0.3	0.3	0.3	0.3	0.3

FIG 5: Median Electrolyte Changes(In mmol/l)

7.2.2 MEDIAN LEVELS FOR POTASSIUM AND PHOSPHATE. (mmol/l)

The two serum electrolytes which showed a significant change were potassium and phosphate.Both started rising on day 1 after adminstration of chemotherapy and reached maximum levels on day 2 and 3 and started falling back to the baseline on day 4 (figure 6).



	Day0	Day1	Day2	Day3	Day4	Day7	Day14
Potassium	4.0	5.1	5.4	5.2	5.1	4.8	4.0
Phosphate	1.1	2.2	2.3	2.3	2.2	2.0	1.3

FIG 6: Median Changes Of Potassium And Phosphate In milimol/litre.

7.3. INCIDENCE OF TLS AMONGST THE STUDY SUBJECTS

Based on increase in serum potassium and phosphate by more than 25% from baseline values 42 patients (37.83%,C.I=31.27-44.29) out of 111 study subjects developed laboratory TLS(figure 7).

There was no change in serum calcium that met the criteria for laboratory TLS while only one patient was diagnosed with TLS based on increase in serum uric acid levels.

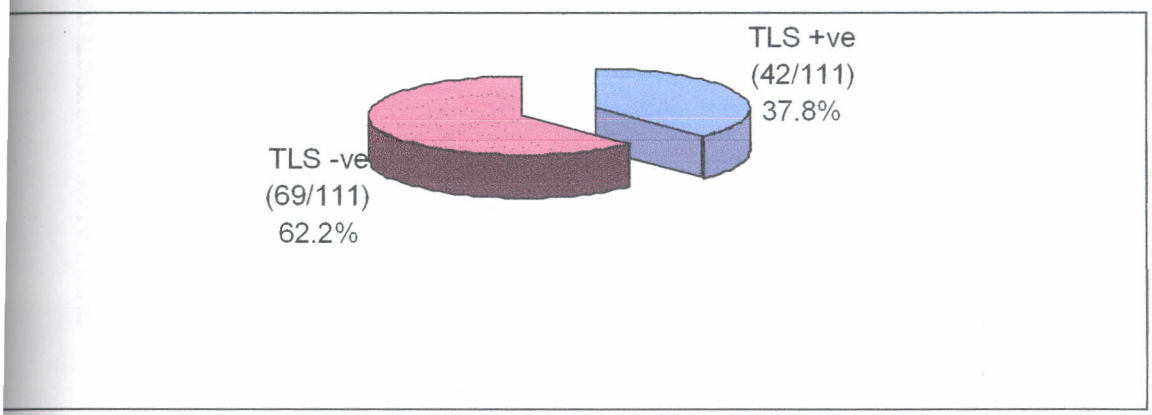


FIG 7: Incidence Of TLS Amongst The Study Subjects

7.4.1. TEMPORAL DETECTION OF TLS

TLS was detected in 50% of the 42 patients on day 1 and by the third day, 95.2% of cases had been detected. Only 2.4% of the cases were detected on day 4. The cumulative percentage by day four was 97.6%(figure 8).

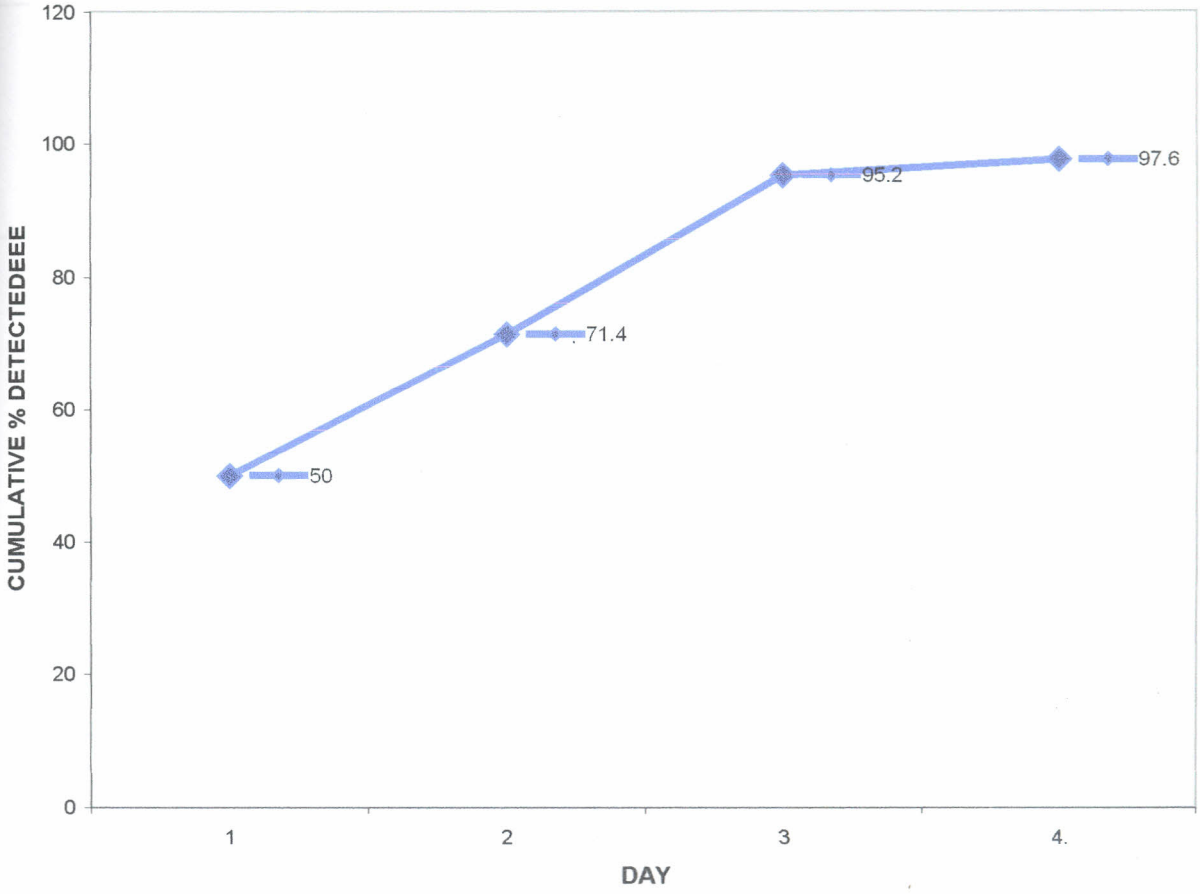


FIG 8:Temporal Trend Of TLS Detection .

7.4.2. TEMPORAL RESOLUTION OF TLS

Resolution of TLS was first noticed on day 2 when 11.9% of patients resolved. By the seventh day, 54.8 %of cases had resolved while.97.7% resolved by the 15th day . Only 2.4% of the cases had not resolved by day 15(figure 9).

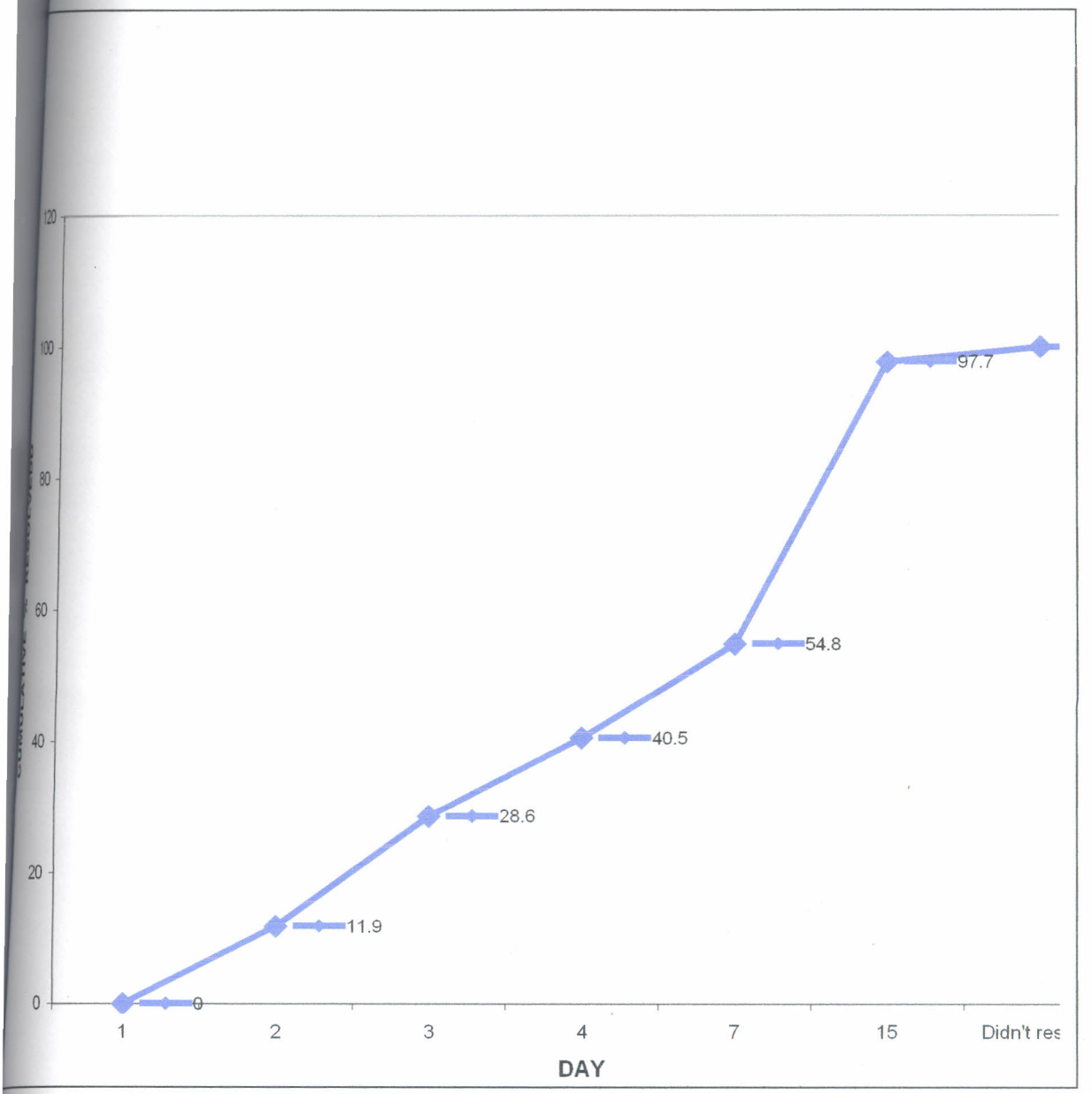


FIG 9: Temporal Trend Of TLS Resolution

75.1. DISTRIBUTION OF SERUM POTASSIUM AMONGST PATIENTS WITH TLS

At baseline, all the 42 patients who developed TLS had serum potassium ranging from 3.0mmol/l to 5.4mmol/l. No patient had values above the laboratory upper normal value of 5.5mmol/l(figure 10a).

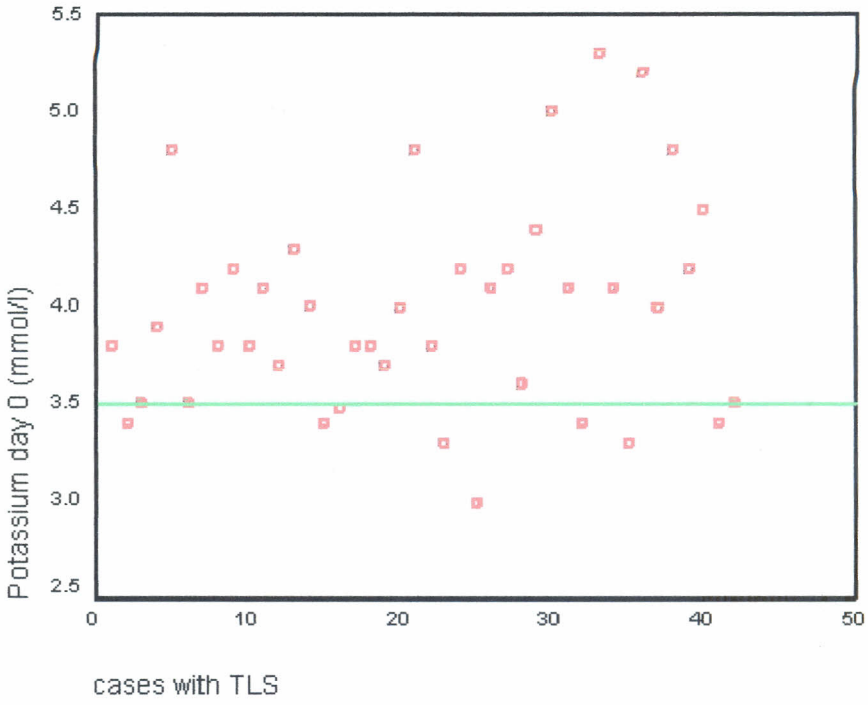


FIG.10a;Distribution Of Serum Potassium At Baseline(day 0)

Red squares represent patients with TLS = 42

Green line represents the laboratory lower limit of 3.5mmol/l.

No patient had serum potassium of 5.5mmol/l therefore there is no upper green line to show the upperr limit of normal.

Only 50 % of patients developing TLS between day 1 to day 3 had elevated potassium levels above the laboratory reference range of 3.5mmol/l to 5.5 mmol/l(*10b to 10d). This distribution means that using laboratory potassium* reference values instead of serial changes will fail to diagnose TLS in 50% of patients.

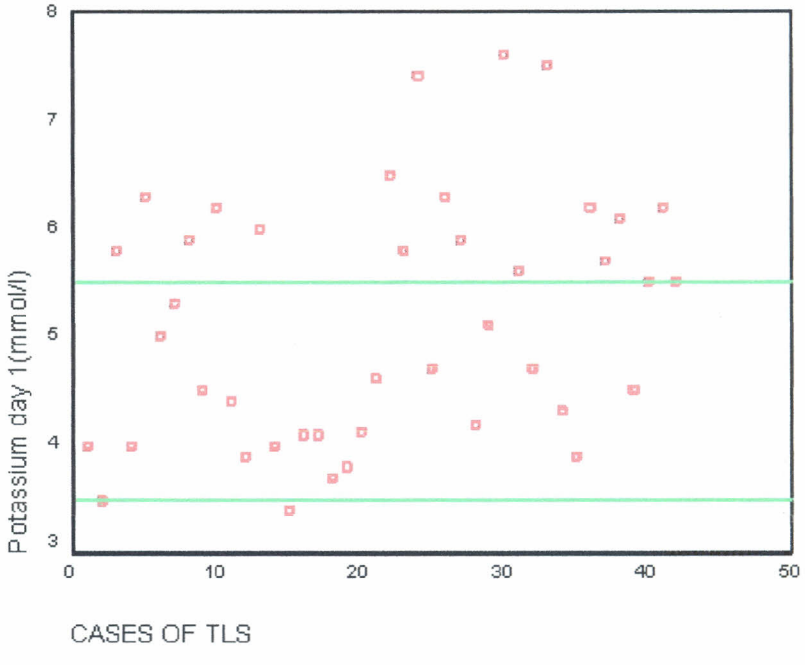


FIG. 10b;Distribution Of Serum Potassium On Day 1.

Green lines represent the normal laboratory reference range of 3.5mmol/l to 5.5mmol/l.

Red squares represent patients with TLS = 42

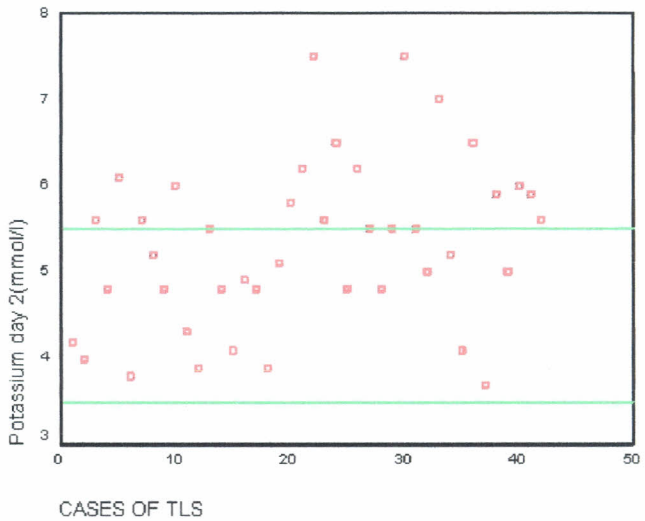


FIG.109c;Distribution Of Serum Potassium On Day 2.

Green lines represent the normal laboratory reference range of 3.5mmol/l to 5.5mmol/l. Red squares represent patients with TLS = 42

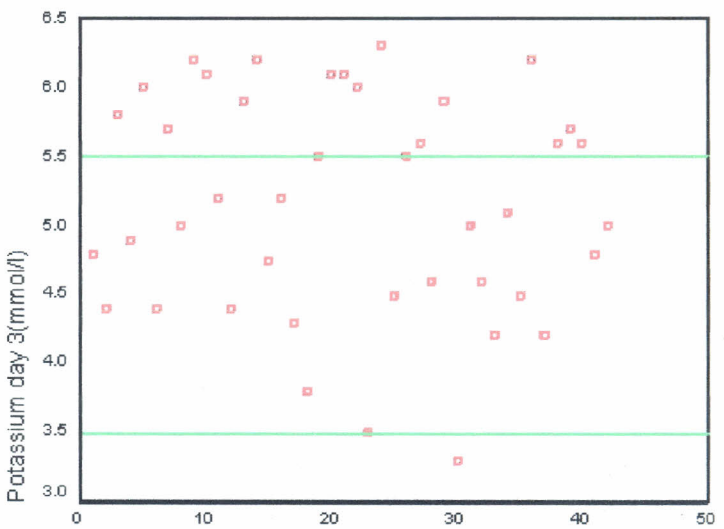


FIG.10d;Distribution Of Serum Potassium On Day 3.

Green lines represent the normal laboratory reference range of 3.5mmol/l to 5.5mmol/l. Red squares represent patients with TLS = 42.

7.5.2. DISTRIBUTION OF SERUM PHOSPHATE IN PATIENTS WITH TLS

At baseline(day 0),only 16.6% of patients had serum phosphate values above the laboratory reference range of 0.8mmol/l to 1.45mmol/l(figure 10e).

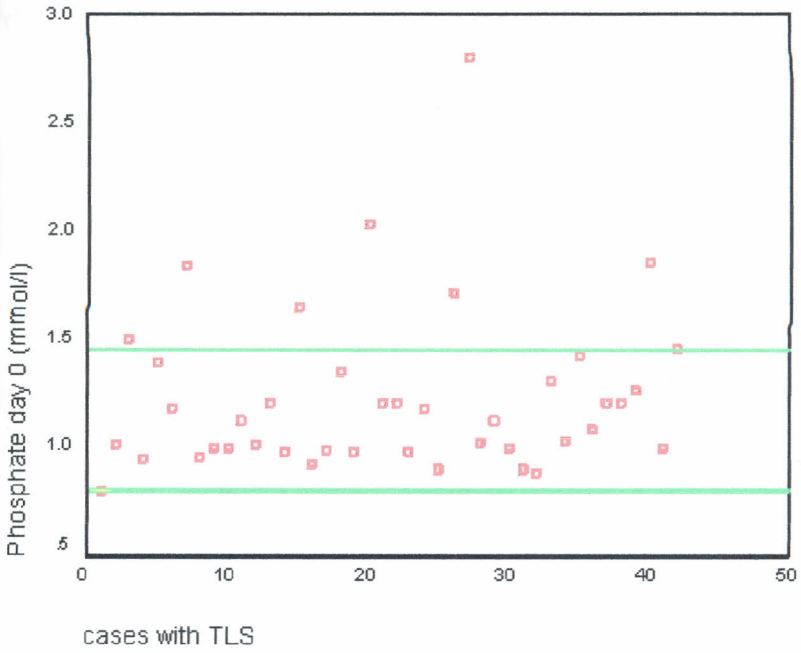


FIG.10e;Distribution Of Serum Phosphate On Day *0(baseline)*

Green lines represent the normal laboratory reference range of 0.8-1.45 mmol/l.

Red squares represent patients with TLS = 42

The distribution of serum phosphate on day 1,2, and 3 above normal laboratory reference values was 86% to 96%(figures 10f,g, and h). This means that 86-96% of patients with TLS had serum phosphates above 1.45mmol/l and so using laboratory reference values instead of serial phosphate changes will fail to diagnose TLS in 4-14 % of patients.This is better than potassium which will fail to detect 50% as previously shown.

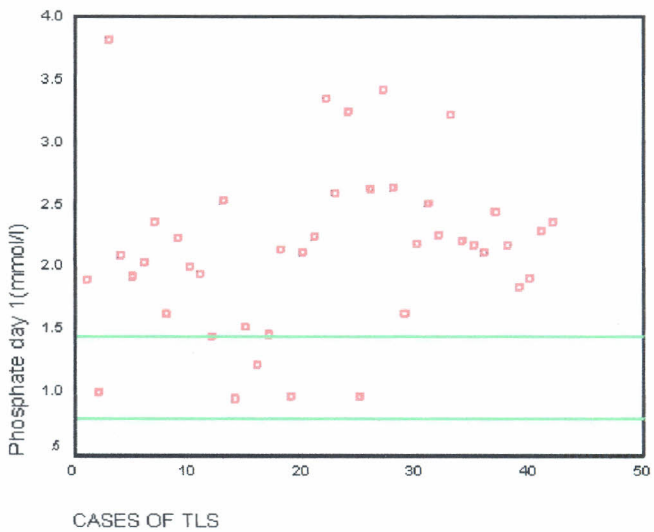


FIG. 10f;Distribution Of Serum Phosphate On Day 1

Green lines represent the normal laboratory reference range of 0.8-1.45 mmol/l.. Red squares represent patients with TLS = 42

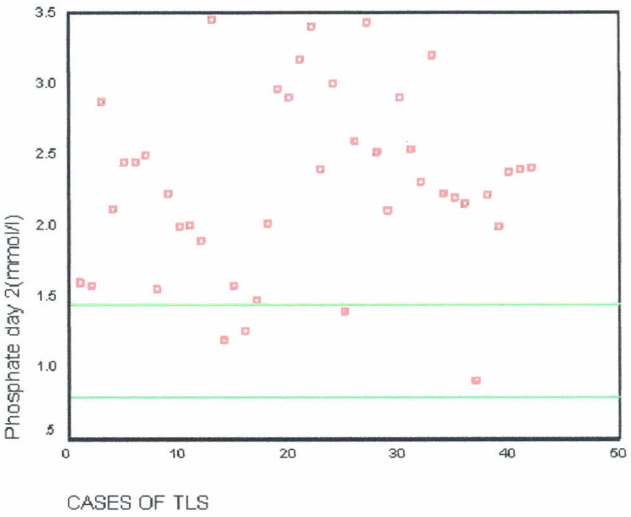


FIG.10g;Distribution Of serum Phosphate On Day 2

Green lines represent the normal laboratory reference range of 0.8-1.45 mmol/l. Red squares represent patients with TLS = 42

Figure 9h

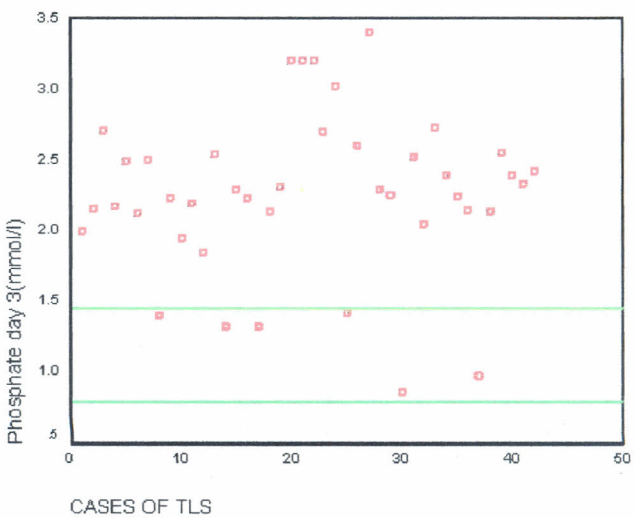


FIG. 9g;Distribution Of Serum Phosphate On Day 3

Green lines represent the normal laboratory reference range of 0.8-1.45 mmol/l. Red squares represent patients with TLS = 42

7.6. TLS DISTRIBUTION ACCORDING TO TYPE OF TUMOUR

No case of TLS was detected in patients with breast cancer while 14 out of 18 patients with non-Hodgkin's lymphoma(77.8%,95% C.I=66.2-90.4) developed TLS (table 5).

TUMOUR	TOTAL NUMBER	TLS POSITIVE	TLS %of TOTAL No. (95% C.I)
Breast cancer	45	0	0
Non-Hodgkin's Lymphoma	18	14	77.8(66.2-90.4)
Chronic Myeloid L	9	7	77.8(62-93.6
Chronic Lymphocytic Leukaemia	8	8	100.0
Hodgkin's Lymphoma	6	4	66.7(45.5-87.9)
Multiple Myeloma	5	2	40.0
Acute Lymphoid Leukaemia	4	3	75
Acute Myeloid Leukaemia	3	2	66.7
Choriocarcinoma	3	1	33.3
Osteogenic sarcoma	2	0	0
Ca Colon	2	0	0
Rhabdomyosarcoma	1	1	100
Ca Ovary	1	0	0
Hepatoma	1	0	0
Fibrosarcoma	1	0	0
Unknown Metastases.	1	0	0
GasroIntestinal Stromal Tumour	1	0	0
TOTAL	111	42	

TABLE 5:Proportion Of Patients Developing TLS By Tumour Type. *Key;95% C.I=95% confidence interval.*

7.6.1. TUMOUR DISTRIBUTION IN PATIENTS WITH TLS

The commonest tumour developing TLS was non-Hodgkin's lymphoma(NHL) comprising 33.3% followed by chronic leukaemias(16.7 %and 19%) (figure 11). No case of TLS was detected in patients with breast cancer although it was the most common tumour in the study population.

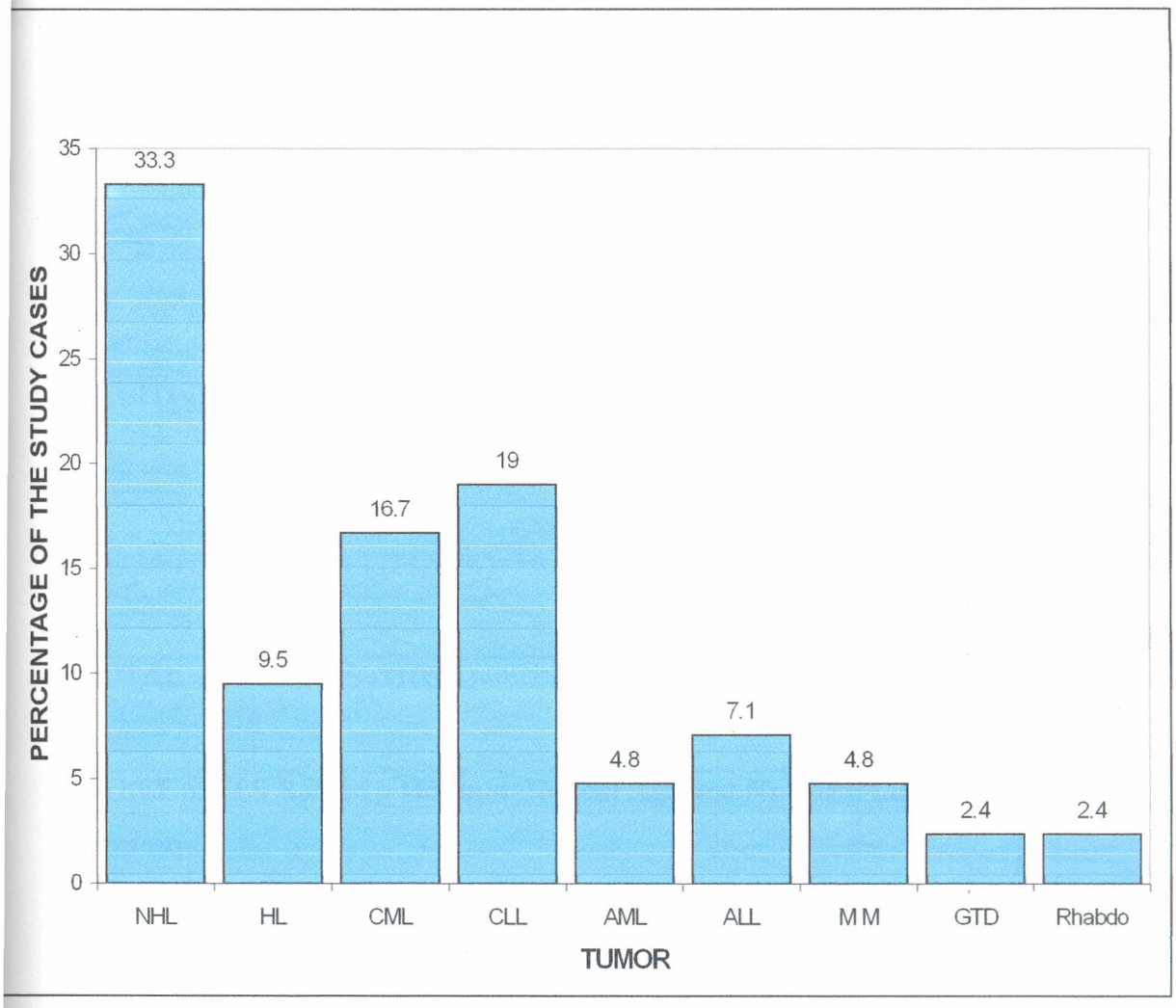


FIG 11: Tumour Distribution In The 42 Patients With TLS

Key. CML=Chronic myeloid leukemia AML=Acute Myeloid Leukaemia Rhabdo =Rhabdomyosarcoma.CLL=Chronic Lymphocytic Leukaemia MM= Multiple myeloma , HL=Hodgkin's lymphoma, GTD= Choriocarcinoma NHL=Non-Hodgkin's Lymphoma,CML= Chronic Myeloid Leukaemia,ALL= Acute Lymphoblastic Leukaemia

7.6.2. TLS RATES IN HAEMATOLOGICAL AGAINST NON-HAEMATOLOGICAL TUMOURS

TLS was detected in 40 out of the 53 patients with haematological tumours(75.47%,95%C.I=66.47-84.47). Only 2 out of 58 patients with non-haematological tumours (3.45%.95% C.I=-1.55-8.45) developed TLS (table 6).

	HAEMATOLOGICAL	NON HAEMATOLOGICAL	TOTAL	P VALUE
POSITIVE	40 (75.47%, 95%C.I= 66.47-84.47)	1 (3.45%,95%C.I = -1.55-8.45)	42	<0.001
NEGATIVE	13 (24.53%)	56 (96.55%)	69	
TOTAL	53 (100%)	58 (100)	111	

TABLE 6: TLS Rates In Haematological Against Non-Haematological Tumours

Key;Haematological refers to lymphomas,leukaemias,and multiple myeloma.

7.6.3. SUBTYPE ANALYSIS OF THE HAEMATOLOGICAL NEOPLASMS

Table 7 shows that 70.83% of patients with lymphoma developed TLS compared to 62.5% of leukaemia patients. However this was not statistically significant.

	LYMPHOMA	LEUKAEMIA	P VALUE
TLS POSITVE	17 (70.83%,95% C.I =59.83-81.83)	15 (62.5%,95%C.I= 50.5-74.5)	0.592
TLS NEGATIVE	*7 (29.2%)*	*9 (37.5%)*	
TOTAL NUMBER	24	24	

TABLE 7. TLS Rates In Patients With Lymphoma And Leukaemia

7.6.4. SUB-TYPES OF NON HODGKIN'S LYMPHOMA

Out of 18 patients with NHL 7 (38.89%) had diffuse large cell lymphoma and all of them developed TLS. However the numbers are inadequate for statistical testing (table 8).

SUB-TYPE OF NHL	Number	TLS +VE	TLS -VE
Diffuse Large cell	7	7 (100%)	0
Burkitt's	3	3 (100%)	0
Small Lymphocytic	4	1 (25%)	3 (75%)
Unclassified	3	2 (66.67%)	1 (33.33%)

TABLE 8. Sub-Types Of Non- Hodgkin's Lymphoma

Key;Unclassified and Unknown metastases refers to tumours of unclear histology that were treated as lymphoma.

7.7. TLS AMONGST PATIENTS WITH KARNOFSKY PERFOMANCE SCORE (KPS) BELOW 70

The functional status of most patients was poor (KPS below 70=68/111). However the difference in incidence of TLS in those scoring 70 and above was not statistically significant (table 9) .

KPS SCORE	≤60	≥70	P VALUE
TOTAL=111	68	43	
TLS POSITIVE	29 / 68 = 42.6%,C.I=34-50)	13 / 43 = 30%.C.I =21%-39%	0.19

TABLE 9: TLS Rates According To KPS

7.8. MORBIDITY AND MORTALITY DATA

Patients with non-Hodgkin's lymphoma received the second course of chemotherapy after 21 days. By then, TLS had resolved and therefore the development of TLS did not interfere with the treatment schedule. In patients who developed hyperkalaemia, eleven were managed conservatively with dextrose and insulin infusion.

No patient was treated for hyperphosphataemia and none required renal replacement therapy.

Two patients died on day 5 and day 6 respectively.The first one was a female aged 21years.She had acute myeloid leukaemia(AML),French-American- British (FAB) type M2 and at the time of death, her serum potassium was 7.4mmol/l.She also had bleeding due to thrombocytopaenia of 10×10^{9} per litre.

The second patient was also female aged 24years.She had abdominal rhabdomyosarcoma and at the time of death, uric acid was 0.45mmol/l and potassium was 5.9mmol/l.This translates to a study case fatality rate of 1.8%

No postmortem studies were done on these patients.

8. DISCUSSION

The incidence of TLS found in this study was 37.8%. At KNH, about 720 patients receive chemotherapy annually.This means that about 273 patients may develop TLS per year. Over 50% of these cases occur on the first day of initiating chemotherapy and by the fourth day, 98% of cases have occurred. If serum potassium, phosphate, uric acid and calcium are measured daily for the first four days after starting chemotherapy, most cases of TLS should be detected early and intervention instituted. It may be more useful to start monitoring within the first 12 hours of administration of chemotherapy instead of waiting for 24 hours because these changes were shown to start much earlier. The main limitation with starting monitoring earlier is the timing because it will require in-patient care for all patients receiving chemotherapy and may not be cost effective.

By end of the first week, about 45% of patients had not recovered from TLS. This is important in patients receiving weekly treatment like acute lymphoblastic leukemia. It is important to assay serum electrolytes before giving the second course of chemotherapy because pretreatment derangement in renal function predisposes patients to development of TLS .

This is the first study in Kenya to determine chemotherapy-related TLS. Although the overall incidence is less than 42% reported by Hande and Garrow at Vanderbit University, Tenessee, (1) it is not surprising because they studied non-Hodgkin's lymphomas alone. When non-Hodgkin's lymphomas in our study were analysed separately, the incidence of TLS was 70.8%. This is consistent with the higher incidence projected before the study commenced. Cohen et al (19) reported an incidence of 38.3% as did Arseneau (20) of 25% using different case definitions. Both studies were done in the 1980s before Hande et al proposed the current definition in 1993. Arseneau used hyperkalaemia alone while Cohen used both hyperkalaemia and hyperuricaemia to define TLS.

In our study, 95.2% of the TLS cases involved haematological malignancies. This is consistent with other studies which have shown that TLS is mainly a complication of chemotherapy for haematological malignancies (1). The factors which predispose haematological malignancies to develop TLS include high chemosensitivity, high mitotic rate, large tumour bulk, and use of intensive chemotherapy protocols.

Published literature on TLS involving non-haematological malignancies is limited (17,28,29,30). In our study, only two patients with non-haematological tumours developed TLS.The first one had metastatic choriocarcinoma and the second had abdominal rhabdomyosarcoma.

All the patients with TLS had consistent increase in serum potassium and phosphate by at least 25%. Both electrolytes are released during cytolysis and formed two parallel curves between day 1 and day 15 as was seen in figure 6. This raises the question whether we can estimate the concentration of potassium from phosphate or phosphate from potassium in patients receiving chemotherapy. If these findings can be reproduced in other studies then it may be possible to relate the two electrolytes.

As shown in figures 10b, c, and d only 50% of patients with TLS from day 1 to day 3 had elevated potassium levels beyond the laboratory reference value of 5.5 mmol/l. In contrast, 86% to 96% of patients with TLS had phosphate elevation above the laboratory reference value of 1.45mmol/l. Using the laboratory reference levels for potassium alone to detect TLS will miss about 50% of cases while phosphate levels alone will miss 4-14%.Therefore serum phosphate was more sensitive to TLS development compared to serum potassium. When the product of plasma calcium x phosphate exceeds 4.6mmol/l to 5.6mmol/l, extraskeletal calcification develops. In this study, the product of plasma calcium x phosphate ranged from 2.53mmo/l to 5.29mmol/l. There was

no secondary hypocalcaemia. No interventions to reduce plasma phosphate were considered.

Only one patient developed hyperuricaemia in this study. She was a 24 year old female with abdominal rhabdomyosarcoma and received single agent doxorubicin therapy. She was not taking allopurinol for TLS prophylaxis. Dann et al(49) reported a case of a 23 year old female with lymphosarcoma who died from TLS despite allopurinol prophylaxis. Unlike the patient in our study who received doxorubicin monotherapy, the patient reported by Dann et al received cyclophosphamide and vincristine .

The absence of hyperuricaemia is unusual because it is believed to be the most commonly observed derangement in patients with chemosensitive tumours (7,8,9,34,). One of the reasons may be the use of allopurinol prophylaxis to prevent TLS in all the patients at risk. However it is known that allopurinol prophylaxis is not 100% protective against development of hyperuricaemia (8). Its routine use could explain the rarity of hyperuricaemia in patients on chemotherapy at KNH. It is also possible that chemotherapy of the majority of lymphomas does not necessarily need routine use of allopurinol for prophylaxis (N.A Othieno Abinya,personal communication). This needs to be tested in a properly controlled study.

No patient had a decline in serum calcium by 25% from baseline. This is because hypocalcaemia occurs secondary to hyperphosphataemia and since the phosphate elevation was moderate, it was not sufficient to cause hypocalcaemia (2).

One patient with recurrent choriocarcinoma developed TLS. She was 31 years old, receiving methotraxate, doxorubicin and cyclophosphamide. Choriocarcinomas are germ cell tumours with a high proliferative rate and high

8.1. GENERALISABILITY OF DATA

This was a hospital-based study and patients recruited were a true representation of patients receiving chemotherapy at KNH. Evidence for similarity is shown by identical baseline characteristics between the included and excluded study subjects in figures 1, 2a, 2b, and tables 2 and 3. Therefore the study findings are generalisable to all patients receiving chemotherapy at KNH. In Kenya, KNH is the main cancer treatment centre and therefore the study findings are generalisable to the rest of the country. However, highly chemosensitive solid tumours like small–cell lung cancer and germ cell tumours were poorly represented and the findings are not generalisable to them.

8.2. THREATS TO VALIDITY

The chances of getting false positive cases of TLS are low because the diagnosis was based on different parameters(serum urate,potassium,phosphate and calcium) recorded on different days(day 1-4). However there is a possibility of false negative cases because tests were done at 24 hour intervals.As shown in figure 4, electrolyte changes following adminstration of chemotherapy start before 24 hours. Such false negatives would only be the transient and minor cases thus posing no threat to the validity of the study results.

8.3. STUDY LIMITATIONS

(1) Patients dropping out because they could not continue coming to the hospital daily. The age, gender and histological tumour-type distribution of these patients was similar to those who completed the study.

(2) TLS in different stages of tumour was not analysed because the available records on staging were inadequate and the results could have been unreliable.

(3) Parameters of clinically manifest TLS such as serum urea, creatinine and Electrocardiographic recording were not collected due to logistical problems.

(4) Chemosensitive solid tumours like small-cell lung cancer and other germ-cell tumours were not represented in this study because cases were not available during recruitment of study subjects.If a similar study is done with a larger number of these chemosensitive tumours, then the incidence of TLS in non-haematological malignancies may be higher.

(5) The effect of different chemotherapy regimes was not analysed because of inadequte numbers.

8.4. CONCLUSIONS

- Tumour lysis syndrome is common at KNH (37.83%) and mainly occurs in haematological malignancies.

- Most cases of tumour lysis syndrome occur on the first day of chemotherapy.

- Hyperkalaemia and hyperphosphataemia are the main manifestations of TLS at KNH.

8.5. RECOMMENDATIONS

- ✓ All patients with haematological malignancies receiving chemotherapy should have their electrolytes monitored for at least the first two days after initiation of therapy.

- ✓ Patients who cannot afford the cost of laboratory analysis of uric acid, calcium, phosphate and potassium could probably be monitored by serum phosphate and potassium alone

- ✓ Record keeping should be improved, so that data on tumour histology, staging, electrolytes, treatment and outcomes become available for retrospective analysis.

- ✓ A comparative study between patients receiving allopurinol prophylaxis and those off allopurinol prophylaxis should be done to document its usefulness in preventing hyperuricaemia in lymphoma patients.

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10. APPENDICES

APPENDIX 1 Client No------

INCIDENCE OF CHEMOTHERAPY -RELATED TUMOUR LYSIS SYNDROME AT KNH.

10.1 PATIENT INFORMATION SHEET

English version

Dear Sir/Madam/Master/Ms

I am conducting a study on Tumour Lysis Syndrome.This letter is to inform you about the study and to seek your support.

Your doctors have told you that the tumour is best treated with chemotherapy . This works by killing tumor cells.

Killed tumour cells may increase some analytes in blood such as potassium, uric acid and phosphate. This is called Tumor Lysis Syndrome (TLS) and interrupts therapy,causes weakness but most patients recover.

We will record your medical history,examine you and collect 2 milliliters of venous blood daily to monitor for TLS occurrence. A total of about 5 samples will be taken from you.

You or your child are being asked to participate in this study because you meet the inclusion criteria.

Benefits of participation:

1. Your participation will provide us with information that may be useful in the treatment of cancer patients in future.

Risks arising from the study: pain during venepuncture but every effort will be made to minimize the pain and ensure sterility.

Your obligations:

1. Remain on standard treatment as instructed by your Doctor.
2. Know that participation in the study is voluntary.
3. Know that you are free to withdraw consent even after recruitment in the study.

My obligations

1. To keep all your personal information confidential.
2. To make available results of the the blood tests to you and your Doctor.

Our contacts:

UNIVERSITY OF NAIROBI

DEPARTMENT OF MEDICINE

Dr N.W BUSAKHALA KNH EXT 44280 (Investigator)

Prof N.A.O ABINYA KNH EXT 43524 (Supervisor)

If you agree to participate in this study please sign the consent form attached.

APPENDIX 2 Client No.....

IINCIDENCE OF CHEMOTHERAPY -RELATED TUMOUR LYSIS SYNDROME AT KNH.

10.2 SUBJECT CONSENT FORM

I,Mr/Mrs/Ms----------

Consent to participate in the study on tumour lysis syndrome as explained to me

by----------

I understand the purpose of the study and conditions of my participation.

Sign---------- -------

Witness----------

Sign----------

Date----------

APPENDIX 3 Client No.....

IINCIDENCE OF CHEMOTHERAPY -RELATED TUMOUR LYSIS SYNDROME AT KNH.

10.2.1 PARENT/GUARDIAN CONSENT FORM

I,Mr/Mrs/Ms ----------, the parent/legal guardian

of----------.

I agree to the above and give consent for my child to be included in these study as explained to me by----------

I understand the purpose of the study and conditions of his/her participation.

Sign---------- -------

Witness----------

Sign----------

Date----------

10.2.2 ASSENT FORM FOR CHILDREN > 12 YEARS

I----------

consent to participate in the study on tumour lysis syndrome as explained to me by----------.

I understand the purpose of the study and conditions of my participation.

Name----------

Sign---------- ----------

Witness----------

APPENDIX 5 Client No.---------

UHUSIANO KATI YA TIBABU YA SARATANI NA MADINI MWILINI KATIKA KNH

10.2.4 IDHINI

Mimi ----------nimeelezwa

kwa ukamilifu **kuhusu utafiti huu, na nimekubali** kwa hiari yangu. Nimemruhusu daktari kufanya utafiti huu kwangu .

Sahihi----------

Tarehe----------

Shahidi ----------

Sahihi----------

APPENDIX 6 Client No.---------

UHUSIANO KATI YA TIBABU YA SARATANI NA MADINI MWILINI KATIKA KNH

10.2.5 IDHINI YA MTUNZAJI WA MTOTO

Mimi----------ni

mzazi/ mtunzaji wa----------

Nimekubali ashiriki katika utafiti huu kama nilivioelezwa na Daktari----------

---

Sahihi----------

Tarehe----------

Shahidi ----------

Sahihi----------

10.2.6 IDHINI YA MTOTO JUU YA MIAKA 12

Mimi ----------nimeelezwa kwa ukamilifu kuhusu utafiti huu, na nimekubali kwa hiari yangu. Nimemruhusu Daktari ----------kufanya utafiti huu kwangu

Sahihi----------

Tarehe----------

Shahidi ----------

Sahihi----------

APPENDIX 7 Client No----------

-

INCIDENCE OF CHEMOTHERAPY -RELATED TUMOUR LYSIS SYNDROME AT KNH.

10.3 PROFORMA FORM

Consent given YES ----------NO----------

Age (Years)----------

Male---------- Female----------

Weight (Kg)----------

Height (M)----------

BSA (M^2)----------

Diagnosis. Histology/ Cytology ----------.

Stage:----------

Karnofsky performance score:----------

Fluid therapy----------Allopurinol----------

Treatment Received Yes---------- No----------

If NO, why ----------

Dose----------

APPENDIX 8

INCIDENCE OF CHEMOTHERAPY -RELATED TUMOUR LYSIS SYNDROME AT KNH.

10.4 LABORATORY FINDINGS

)AY	POTASSIUM MMO L/L	PHOSPHATE MMO/L	CALCIUM MMOL/L	URIC ACID MG/DL
0				
1				
2				
3				
4				
7				
15				

APPENDIX 9

INCIDENCE OF CHEMOTHERAPY -RELATED TUMOUR LYSIS SYNDROME AT KNH.

10.5 KARNOFSKY PERFORMANCE INDEX

Performance Status	Functional Capability of Patient
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or do active work.
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled,hospitalization is indicated although death is not imminent
20	Very sick, hospitalization necessary, active supportive treatment necessary
10	Moribund,fatal processes progressing rapidly
0	Dead

APPENDIX 10

INCIDENCE OF CHEMOTHERAPY -RELATED TUMOUR LYSIS SYNDROME AT KNH.

10.6 BIOCHEMICAL ANALYSES

POTASSIUM will be analysed based on the potential difference between a potassium-specific ion selective electrode and a reference electrode in plasma containing potassium.

UREA; Urea is hydrolyzed with urease ,and the ammonium ion formed is reacted with phenol and hypo chlorite in alkaline medium to form iodophenol. Nitroprusside is used to catalyze the reaction.Absorbence of iodophenol is measured at 560 nm.

CREATININE;Creatinine in a protein- free supernatant of plasma or serum is reacted with alkaline picrate to form a color complex whose intensity is measured at 510nm.

URIC ACID;Uric acid is oxidized in the presence of uricase to allantoin and hydrogen peroxide.Hydrogen peroxide then reacts with ethanol to form acetaldehyde.Acetaldehyde then reacts with NAD+ to produce acetate and NADH. Increase in absorbance is measured at 340nm and uric acid concentration is measured from a calibration curve.

CALCIUM Cresolphthalein forms a red chromophore with calcium in alkaline solution.This is measured at a wavelength between 570-580 nm..

ALBUMIN

Albumin and bromocresol green are bound at pH 4.2 and absorption of the bromocresol-albumin complex measured spectophotometrically at 628nm.

PHOSPHATE

Trichloroacetic acid liberates inorganic phosphates from ligands in plasma.This is mixed with ammonium molybdate in acid solution to form ammonium phosphomolybdate. Hydrochloric acid is added and the blue color measured spectrophotometrically.

APPENDIX 11

INCIDENCE OF CHEMOTHERAPY -RELATED TUMOUR LYSIS SYNDROME AT KNH.

10.7. FLOW CHART FOR PATIENT RECRUITMENT