International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2020; 3(1): 242-247
Received: 18-11-2019
Accepted: 22-12-2019

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# To study levels of serum lactate dehydrogenase and serum uric acid in patients suffering from Leukemias

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**DOI:** https://doi.org/10.33545/pathol.2020.v3.i1d.181

**Abstract**
**Background:** In India, Leukemia continues to be the largest contributor to cancer related mortality in children. Once the diagnosis of leukemia is suspected, a rapid evaluation and initiation of appropriate treatment is necessary. In addition biochemical test such as serum lactate dehydrogenase (LDH) activity and uric acid concentration have side by side gained importance in monitoring the prognosis of leukemia, especially during the phase of treatment. AIM: To evaluate serum lactate dehydrogenase and serum uric acid levels in patients suffering from leukemias.
**Material and Methods:** The study was based on fifty patients of leukemia- acute or chronic, lymphoid or myeloid, diagnosed as a case of leukemia, both male and female, irrespective of their age attending out-patient Department or admitted in various wards of Government Medical College and Hospital, Amritsar were taken and their serum LDH and serum uric acid levels were estimated. Informed consent of the patient was taken. All newly diagnosed leukemia cases irrespective of their age and sex with no previous history of taking any chemotherapeutic drugs were included in the study. Quantitative estimation of serum lactate dehydrogenase is estimated using LDH (P-L) kit with normal reference values Serum of 230- 460 U/L at 37 °C and quantitative estimation of serum uric acid was carried out using *in vitro* diagnostic kit (IVD) and enzymatic calorimetric method (Trinder) in clinical chemistry analyzers.
**Results:** Mean serum uric acid and Mean LDH activity in study population was found to be 7.69±1.02 mg/dl and 794.07±227.62 IU/L respectively. Maximum rise in serum uric acid concentration was observed in AML type while Maximum rise in serum uric acid concentration was observed in ALL type. Both mean serum LDH concentrations and mean serum uric acid concentrations with TLC Levels in leukemic patients, we observed a strong correlation between increased TLC levels. On correlation analysis association between it was observed that the relation between serum uric acid and serum LDH would be considered statistically significant.
**Conclusion:** We can conclude that patients presenting with raised TLC along with hypercellular bone marrow and presenting with increased serum uric acid and LDH concentrations usually show poor prognosis in comparison to other leukemic patients.Thus continuous biochemical monitoring of serum LDH activity and uric acid concentration can play an important role in monitoring the prognostic aspect of the disease. Both serum uric acid and LDH measurement are easily available in laboratory and much cheaper parameters to assess disease progression.

**Keywords:** serum lactate dehydrogenase, serum uric acid and Leukemias

## Introduction
Leukemia are defined as malignant disorders of the hematopoietic stem cell compartment, characteristically associated with increased numbers of white cells in the bone marrow and peripheral blood [1]. It exceeds to be a cause of death in comparision to many of the acute communicable diseases because of its fatal character [2, 3].
In India, Leukemia continues to be the largest contributor to cancer related mortality in children [4]. Due to the lack of any nationwide leukemia screening program, the majority of the population of India is still unaware of this blood disorder. ALL is predominantly a disease of children, with highest incidence in children between the ages of 2 and 6. ALL has a second peak incidence in the elderly population. The rate of AML is somewhat higher in males than females. Chronic leukemias, both CLL as well as CML occur mainly in middle and old age [5].

Once the diagnosis of leukemia is suspected, a rapid evaluation and initiation of appropriate treatment is necessary because of its overwhelming impact on prognosis in terms of achieving complete remission or providing a better quality of life for a longer period of time. In addition, biochemical test such as serum lactate dehydrogenase (LDH) activity and uric acid concentration have side by side gained importance in monitoring the prognosis of leukemia, especially during the phase of treatment [5].

Serum Lactate dehydrogenase (LDH) plays a major role in hematological malignancies. LDH activity is present in all cells of the body and is invariably found in the cytoplasm of the cell. As cells die, their LDH is released and finds its way into blood. Hence almost all hematological malignancies show elevated levels of serum LDH. It is also useful in the assessment of tissue breakdown in general [6, 7]. There is a good relationship between neoplasia and increased serum lactate dehydrogenase (LDH) level.

Another biological substance, serum uric acid (UA) is also found to be raised in patients with haematopoietic malignancies like leukemias due to increase in cell turnover of malignant cell population. Uric acid has paradoxically been found to have the characteristic of being an antioxidant in the extracellular environment, whilst having pro-oxidative effects in the intracellular environment [9, 10]. As an antioxidant, uric acid acts as a scavenger of oxygen radicals, and thus may serve to reduce carcinogenic reactive oxygen species (ROS) [11, 12]. ROS are carcinogenic as they increase the mutation rate in cells, and therefore increase their oncogenic potential [12, 13]. As a pro-oxidant, uric acid contributes to tumourigenesis by entering normal cells and promoting tumour cell proliferation, migration, and survival, mediated by ROS and inflammatory stress [14].

Leukemia patients need to have rapid and appropriate treatment because of it's overwhelming impact on prognosis in terms of achieving complete remission and a better quality of life. In addition to haematological and bone marrow examination, biochemical test such as serum lactate dehydrogenase and serum uric acid levels have gained importance in monitoring the prognosis of leukemia especially during the phase of treatment. Hence, serum uric acid and LDH estimations, which are easily available and cost effective, have gained considerable appreciation as valuable prognostic markers of leukemia.

Therefore, we aimed a study to evaluate levels of serum lactate dehydrogenase and serum uric acid in patients suffering from leukemias.

## Material and Methods

The present study was carried out on patients admitted in different units of Medicine and Pediatrics, department of Government Medical College & Hospital, Amritsar, after approval from institutional thesis and Ethics committee.

The study was based on fifty patients of leukemia- acute or chronic, lymphoid or myeloid, diagnosed as a case of leukemia, both male and female, irrespective of their age attending out-patient Department or admitted in various wards of Government Medical College and Hospital, Amritsar were taken and their serum LDH and serum uric acid levels were estimated. Informed consent of the patient was taken. All newly diagnosed leukemia cases irrespective of their age and sex with no previous history of taking any chemotherapeutic drugs were included in the study. While patients on treatment and those who did not give consent for the study were excluded from the study.

**Collection of blood sample:** 3ml of blood was collected from selected subject's ante cubital vein by means of a disposable syringe and needle in a sterile empty vial (SEV) with all aseptic and antiseptic precautions. The blood collected in SEV was allowed to clot for 30 minutes in a clean dry test tube and was subjected to centrifugation in a clinical centrifuge machine at 3000 rpm for 3 minutes to separate the serum. The separated serum was used to estimate serum LDH and serum uric acid levels. Serum with slightest evidence of hemolysis was discarded.

**Estimation of serum lactate dehydrogenase:** Quantitative estimation of serum lactate dehydrogenase was carried out using LDH (P-L) kit with normal reference values Serum of 230- 460 U/L at 37 ℃

**Estimation of serum uric acid:** Quantitative estimation of serum uric acid was carried out using *in vitro* diagnostic kit (IVD) and enzymatic calorimetric method (Trinder) in clinical chemistry analyzers. Reference values used as a guideline for Serum uric acid are, in Males (3.5-7.2 mg/dL) and in females (2.6-6.0 mg/dL).

**Statistical Analysis:** Statistical analysis of the data was performed by using Microsoft Excel software. ANOVA test was applied for statistical analysis and Tukey HSD Post-hoc Test was applied for correlation analysis. '*p*' value of less than or equal to 0.05 was considered significant.

## Results

A total of 50 cases were included in the present study with maximum number of cases in the 21-30 years age range with a mean of 42.98±20.44 years. Male population predominated with males accounting for 56% and females 44% of the study population.

In the present study CML was the most common type of leukemia encountered (52%), followed by AML (20%), CLL (16%) and lastly ALL (12%). (Figure 1)

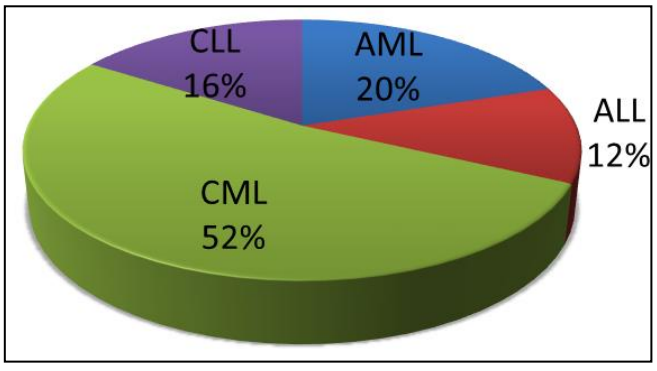



**Fig 1:** Graph showing different types of Leukemia included in study

On haematological examination, highest Hb levels were seen in CLL type while Lowest Hb were seen in ALL type of leukemias. Average TLC observed was 48660 ($mm^3$). In general low TLC levels are seen in acute type of leukemias while chronic leukemias showed larger TLC values. On basis of hypercellularity, Hypercellular bone marrow is seen

in 90% cases of AML, 80% of ALL cases, 84.5% in CML cases while only 50% in CLL cases.

Mean serum uric acid in study population was found to be 7.69±1.02 mg/dl with 66% of the leukemic patients with serum uric acid concentration >7.2 mg/dl, 34% cases with serum uric acid concentration within upper limit of normal range i.e <7.2 mg/dl. (Figure 2)

Maximum rise in serum uric acid concentration was observed in AML type, followed by CML, ALL and lastly CLL type of leukemias. The difference in the mean serum uric acid concentrations among all the 4 types were found to be statistically significant ($p$<0.001). (Table 1)

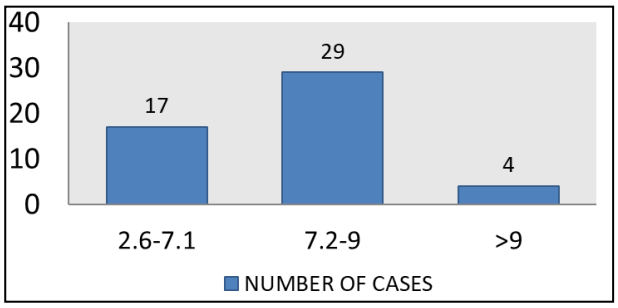



**Fig 2:** Distribution of sample according to uric acid levels in study sample. (n=50)

**Table 1:** Mean Serum Uric Acid Concentration in Different Types of Leukemias.

| Mean Serum uric acid | Type of Leukemia | | | | P value* |
|---|---|---|---|---|---|
| | AML (N=10) | ALL (N=6) | CML (N=26) | CLL (N=8) | <0.001* Significant |
| | 8.83±0.48 | 6.88±0.70 | 7.87±0.66 | 6.26±0.42 | |

On Tukey HSD Post-hoc Test (95% CI) for comparison of mean serum uric acid concentrations within groups, it was observed that difference in mean serum uric acid concentrations between individual types (AML & ALL, AML & CML, AML & CLL, ALL & CML and CML & CLL) were statistically significant ($p$<0.001). While on contrary, difference in mean serum uric acid concentrations between ALL & CLL type of leukemias was not found to be statistically significant ($p$<0.331; Diff=-0.6200, 95% CI= -1.5874 to 0.3474).

Mean LDH activity in the study population came to be 794.07±227.62 IU/L. 90% of cases with leukemia had serum lactate dehydrogenase activity above the normal range, while only 10% cases were within normal range (230-460 IU/L). (Figure 3). Maximum rise in serum uric acid concentration was observed in ALL type, followed by CML, AML and lastly CLL type of leukemias. The difference in the mean serum uric acid concentrations among all the 4 types were found to be statistically significant ($p$<0.001). (Table 2) Further, on Tukey HSD Post-hoc Test (95% CI) for comparison of mean serum LDH concentration within groups, it was observed that difference in mean serum LDH concentration between individual types (AML & ALL, AML & CLL, ALL & CML, ALL & CLL and CML & CLL) were statistically significant ($p$<0.001). While on contrary, difference in mean serum uric acid concentrations between AML & CML type of leukemias was not found to be statistically significant ($p$< 0.924; Diff=35.8900, 95% CI=-118.2280 to 190.0080)

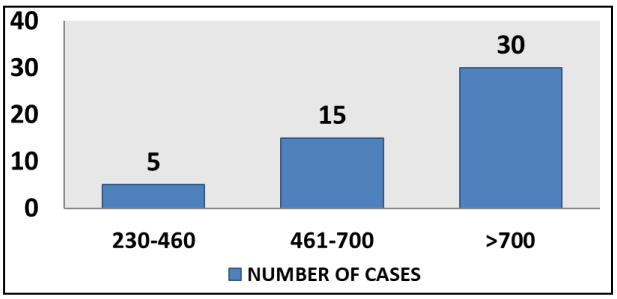


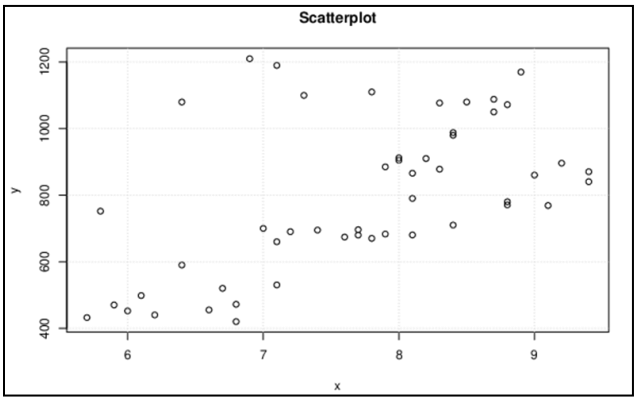

**Fig 3:** Distribution of sample according to ldh levels in study sample. (n=50)

**Table 2:** Mean Serum Ldh Levels (Iu/L) In Different Types of Leukemias

| Mean Serum LDH Activity (IU/L) | Type of Leukemia | | | | P value* |
|---|---|---|---|---|---|
| | AML (N=10) | ALL (N=6) | CML (N=26) | CLL (N=8) | <0.001 significant |

On correlating both mean serum LDH concentrations and mean serum uric acid concentrations with TLC Levels in leukemic patients, we observed a strong correlation between increased TLC levels (11000-100000 and above 100000 TLC Levels). By normal standards, the association between these variables was considered statistically significant.

The spherman's rank correlation coefficient (rho-coffiecient) to see the association between serum uric acid and serum LDH came to be $r_s$ = 0.55755. Therefor**e** By normal standards, the association between the two variables was considered as statistically significant.




X axis = serum uric acid; Y axis= serum LDH levels

**Fig 4:** Scatter plot diagram showing correlation of Serum LDH and Serum Uric Acid in Leukemic Patients

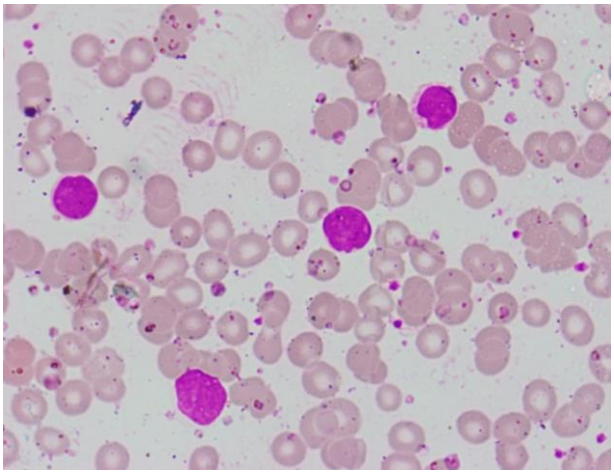


**Fig 1:** Photomicrograph of acute lymphocytic leukemia. Peripheral blood film showing large cells with high nucleo-cytoplasmic ratio, coarse nuclear chromatin and indistinct nucleoli (Leishman stain, 1000X).

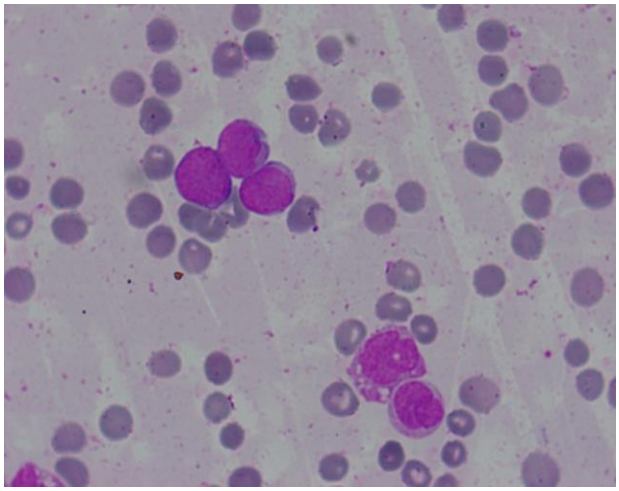


**Fig 2:** Photomicrograph of acute myeloid leukemia. Peripheral blood film shows large cells with high nucleo-cytoplasmic ratio, moderate cytoplasm, coarse chromatin and prominent nucleoli (Leishman stain, 1000X).

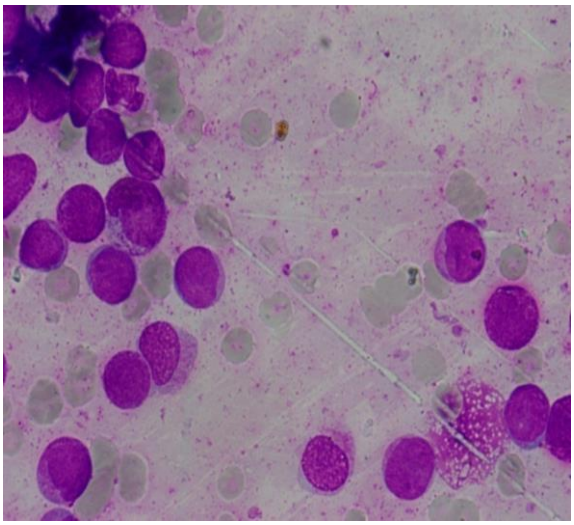


**Fig 3:** Photomicrograph of acute myelogenous leukemia. Bone marrow aspirate smear showing myeloblasts – large blasts with moderate amount of pale basophilic granular cytoplasm, oval to slightly indented nuclei and prominent 2 to 4 nucleoli ( Leishman stain, 1000X)

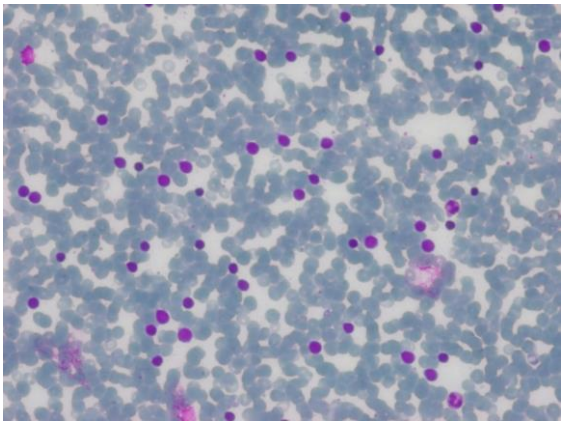


**Fig 4:** Photomicrograph of chronic lymphocytic leukemia. Peripheral blood film showing small mature lymphocytes with condensed chromatin(Leishman stain, 400X).

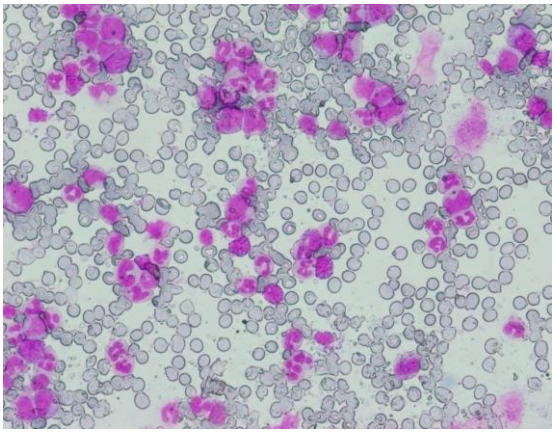


**Fig 5:** Photomicrograph of chronic myelogenous leukemia. Peripheral blood film showing leukocytosis with all stages of myeloid cells from blast cell to neutrophils and basophils (Leishman stain, 400X).

## Discussion

The present cross-sectional study was carried out among 50 leukemia patients to study their serum uric acid and LDH levels.

In the present mean age of leukemic patients was 42.98±20.44 years with male predominance. Various authors who showed concordance in age range similarity were Saharia GK *et al.* [5], Jacob F. *et al.* [15], AK Siraj *et al.* [16] and S. Ghosh *et al.* [17]. Male predominance was also reported by authors like Yiu A *et al.* [18] and Saharia GK *et al.* [5] which is also in similarity with our study.

CML was the most common type of leukemia encountered (52%) in our study while ALL (12%) was least common. In CML type a mean age of 43.3±14.72 years was observed while in ALL type it was 12.5±7.23 years. Further, lowest Hb levels were seen in ALL type of leukemia while maximum was seen in CML type of leukemia. In general, Low TLC levels were seen in acute type of leukemia while Chronic leukemia showed larger TLC values.

On basis of bone marrow cellularity, leukemic patients in our study were divided into hypocellular type, normocellular type and hypercellular type. Majority of cases in the study population were Hypercellular type. Hypercellular bone marrow was predominantly seen seen in AML, ALL and CML cases while in CLL only 50% cases were hypercellular.

Mean serum uric acid concentration in leukemic patients as observed in our study was 7.69±1.02 mg/dl. Saharia GK *et al*. on contrary reported that 83.3% of cases with leukemia have serum uric acid concentration above the normal range with the mean uric acid level being 8.92 mg/dL. The probable cause of increase serum uric acid level in the study group is due to increased nucleic acid catabolism due to increased turnover of malignant cells resulting in increased purine catabolism [5].

Maximum rise in serum uric acid concentration was observed in AML type, followed by CML, ALL and lastly CLL type of leukemia. The difference among all the 4 types were also found to be statistically significant ($p$<0.001). Compareable to our results, Yamauchi *et al*. in their study reported that only 14.3% of the patients had hyperuricemia, although the UA should reflect the burden of AML blasts or proliferating potential [19].

Inai K *et al*. reported that only 20% of patients with AML in their study presented with hyperuricemia at time of diagnosis [20]. Tsimberidou *et al*. evaluated the prognostic significance of several parameters, including UA, in 1,180 patients with AML. In their multivariate analysis, UA greater than the upper limit of normal, and lactate dehydrogenase >1.5-times the upper limit of normal, were one of the top five adverse independent factors predicting poorer survival in patients >60 years [21].

Our results showed that men serum uric acid concentration varied in different types of leukemia with in AML type showing 8.83 mg/dl, ALL type showing 6.88 mg/dl, CML type showing 7.87 mg/dl and CLL type showing 6.26 mg/dl. The difference in mean serum uric acid concentrations between individual types namely AML & ALL, AML & CML, AML & CLL, ALL & CML and CML & CLL were statistically significant ($p$<0.001). While on contrary, difference in mean serum uric acid concentrations between ALL & CLL type of leukemia was not found to be statistically significant. Further on correlating mean serum uric acid concentrations with TLC Levels in leukemic patients, within our study, we observed a strong correlation between increased TLC levels (11000-100000 and above 100000 TLC Levels).

Krakoff & Balis mentioned in their study that the differences in uric acid production between the two types of chronic leukemia was justified on basis of two pathways of uric acid production, the increase in uric acid production in chronic granulocytic leukemia resulting from increased nucleic acid "turnover" and the attendant enhancement of de *novo* purine biosynthesis and the postulated "recycling" of polynucleotides in chronic lymphocytic leukemia with normal uric acid production [22].

Mean LDH activity in the leukemic patients came to be 794.07±227.62 IU/L. It was observed that 90% of cases with leukemia have serum lactate dehydrogenase activity above the normal range, while only 10% cases were within normal range (230-460 IU/L). Our results were in similarity to Saharia GK *et al*. [5], Emad A Al-Saadoon *et al*. [23] and Hafiz MG *et al*. [24]. Who also reported similar findings.

Field M *et al*. [65] explained this increased activity on basis that under rapid proliferation and immaturity of tumor cells, LDH is released due to multiple cytokine activity and cell membrane damage. Any change in LDH level in blood is a reflection for the presence of cell damage. This change may be due to an altered amount of the enzyme forming tissue, as defect in rate of enzyme synthesis, or due to defect in the permeability of the cell member as a result of physiological stress. Our results showed that Maximum rise in serum LDH concentration was observed in ALL type, followed by CML, AML and lastly CLL type of leukemia. The difference in the mean serum LDH concentrations among all the 4 types were found to be statistically significant ($p$<0.001). In concordance, Walaa Fikry ME [25] and Kornberg and Polliack [26] also reported similar results from their studies. Anthony DH *et al*. [27], stated that there was correlation between LDH activity and acute leukemia subtypes.

Our results showed that men serum LDH concentration also varied in different types of leukemia with in AML type showing 796.88 IU/dl, ALL type showing 1073.7 IU/dl, CML type showing 832.77 IU/dl and CLL type showing 455 IU/dl. On comparison of mean serum LDH concentration within different types of leukemia, it was observed that difference in mean serum LDH concentration between AML & ALL, AML & CLL, ALL & CML, ALL & CLL and CML & CLL were statistically significant ($p$<0.001). While on contrary, difference in mean serum uric acid concentrations between AML & CML type of leukemia was not found to be statistically significant.

Further on correlating mean serum LDH concentrations with TLC Levels in leukemic patients within our study population, we observed a strong correlation between increased TLC levels (11000-100000 and above 100000 TLC Levels). In similarity to ours Walaa Fikry ME [25] also reported similar results. In yet another such study by Golam H *et al*. [28] and Emad *et al*. [23], higher serum LDH levels correlated significantly with higher leukocytes counts and blast cells. Lastly, on correlation analysis to find an association between the two variables, it was observed that the relation between serum uric acid and serum LDH would be considered statistically significant as both LDH and uric acid levels may be elevated due to rapid cell turnover.

## Conclusion

Leukemias are still a challenge in present world due to its high mortality and morbidity. Early diagnosis and thus early therapy may help in increasing life expectancy of leukemic patients to some extent. Our results demonstrate that AML type of leukemia with high cell count showed maximum rise in serum uric acid concentration followed by CML Type in blastic crisis. Also highest rise in serum LDH concentration was observed in ALL Type with high cell count followed by CML type in blastic crisis.

Therefore, from our results we can conclude that patients presenting with raised TLC along with hypercellular bone marrow and presenting with increased serum uric acid and LDH concentrations usually show poor prognosis in comparison to other leukemic patients.Thus continuous biochemical monitoring of serum LDH activity and uric acid concentration can play an important role in monitoring the prognostic aspect of the disease. Both serum uric acid and LDH measurement are easily available in laboratory and much cheaper parameters to assess disease progression.

However, we are constrained by the smaller sample size and time limit and longer duration studies with larger sample size might throw more light and help in better management of Leukemia patients.

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