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ORIGINAL ARTICLE

Evaluation of Plasma Level of Anticoagulant Proteins (Protein C, S and Anti Thrombin III) in Patients with Acute Lymphoblastic Leukemia

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Abstract

Background: **Acute lymphoblastic leukemia (ALL) is related to many coagulation abnormalities like hemorrhage & thrombosis.**

Objectives: **Research was to assess role of plasma activity levels of anticoagulant proteins in studied cases with acute lymphocytic leukemia.**

Patients and techniques: **We researched thirty patients with confirmed ALL admitted in EL hussin or Said galal Hospital and twenty apparently healthy as control group. Protein C, Protein S & Anti thrombin III are measured by coagulation analyzer (STAGO).**

Results: **The mean activity levels of protein C (P = zero), Protein S (P = zero) & Anti thrombin III (P = zero) are highly significant lower in studied cases group compared to control group.**

Conclusion: **The hypercoagulability state in ALL patients may attribute to the low level of protein C, protein S & Anti thrombin III.**

Keywords: Acute lymphoblastic leukemia, Anti thrombin III, Protein C, Protein S, Thrombosis

1. Introduction

Acute lymphoblastic leukaemia is malignant disorder that develops from B- (eighty−eighty five percent) or T-cell (fifteen-twenty percent) hematopoietic precursors; acquisition of series of genetic aberrations causes impaired maturation, with differentiation arrest & abnormal proliferation. As result, leukemic cells accumulate in both bone marrow, where they suppress physiologic hematopoiesis, & extramedullary places.[1]

ALL is commonly associated with children, however adults account for significant proportion of cases.[2]

Activated protein C is vitamin K-dependent glycoprotein deduced from liver's protein C zymogen, which interacts with thrombomodulin & endothelial protein C receptor.[3]

APC works primarily by inactivating coagulation factors V a & VIII, which are required for efficient thrombin generation & factor X activation.[4]

Protein S is vitamin K-dependant glycoprotein, is cofactor for protein C system. It is synthesized by hepatocyte, endothelial cells, & megakaryocyte. It circulates in 2 forms: forty-fifty percent present as free form, remainder bound to complement component, the C4b-binding protein; free form has activated protein co factor activity.[5]

Protein S functions as cofactor to activated protein C in regulation of both factor V a (FV a) & factor VIII a (FVIII a).[3]

Ani thrombin III is glycoprotein created by liver that belongs to serine protease inhibitor family. It is primary physiological anticoagulant that

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irreversibly neutralises thrombin & factors Xa & Xia by forming complexes in responses speeded up by heparin or heparin sulphate surface.[6]

2. Patients & techniques

This study were carried on (thirty) cases with acute lymphocytic leukemia (early diagnosed from 2 weeks) and (20) apparently healthy control subjects. The patients were selected from those admitted to hematology unit of El Hussin or Galal Hospital. An informed consent is got from all subjects patient prior to their enrollment in research.

This subject is classified into 2 groups: Group 1 (patient group):involved (30) patient with acute lymphocytic leukemia (early diagnosed from 2 weeks) their age ranged from 2 to 81 year with a mean value 33.77 ± 21.21, they were 10 female and 20 male with a male female ratio 2:1. Group 2 (control group): included (20) patient apparently healthy, there age range from 19 to 67 year with a mean value 34.65 ± 12.55, they were 4 female and 16 male with a male female ratio 4:1.

Inclusion criteria: Patients with ALL (at early diagnosed from 2 weeks).

Exclusion criteria: Patients with leukemia other than ALL.

Studied cases & controls are exposed to subsequent clinical & laboratory researches:

(1) **Detailed history**: Containing years old, gender, & attendance of leukemia-associated symptoms (fever, easy fatigability, bleeding tendency & bone ache).
(2) **Clinical examination:** General & local test containing test of the liver, spleen & lymph node.
(3) **Laboratory investigation:** Routine investigation: Complete blood picture (CBC): including hemoglobin concentration, platelets count & white blood cells count Performed by automated cell counter. Peripheral blood films were stained with leishman stain & tested for recognition of blast cells and their percent. Liver function test and kidney function test performed by Biomajesty (enzymatic &calorimetric assay) or vitros 4600 (dry chemistry). Investigation for diagnosis of acute leukemia (for patient only): Bone marrow aspiration smears: for morphological diagnosis of acute lymphoblastic leukemia. Immunophenotyping: for acute lymphoblastic leukemia. c- Investigation of coagulation profile: Plasma activity level of anticoagulant proteins (protein C percent, protein S percent & Anti thrombin III %) in patient of leukemia & control group by stago analyzer performing clotting (chromogenic &immunological assay).

2.1. Sampling

Random peripheral blood samples from each patient &control (about 6.0 ml) will be collected under complete aseptic condition and divided into:

2 ml of blood was taken into vacutainer tubes containg tri −sodium citrate 1/9 by volume for coagulation profile parameter (protein C, S & Anti thrombin III), 2 ml of blood is taken on ethylene daimine tetra-acetic acid (EDETA) Tube for Complete blood picture (CBC), the residual blood was taken into plain tube for serum separation for liver and kidney function tests.

2.2. Statistical analysis

Data are collected, revised, & entered into SPSS version twenty. Means, medians, standard deviations, numbers, & percentages were used to express findings. Qualitative data were compared using Chi-square, whereas quantitative data with parametric distribution were compared using 1 way ANOVA, with confidence interval set to 95% & approved margin of error set to five percent. As result, p value is deemed important at level of <0.05.

Table 1. Comparing among control group & patients groups concerning age & sex.

	Control group	Studied cases group	Exam value	*P* value	Sig.
	Number = 20	Number = 30			
Years old					
Mean ± SD	34.65 ± 12.55	33.77 ± 21.21	0.167[b]	0.868	NS
Range	19–67	2–81			
Sex					
Female	4 (20.0%)	10 (33.3%)	1.058[a]	0.304	NS
Male	16 (80.0%)	20 (66.7%)			

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: greatly significant.
[a] Chi-square test.
[b] Independent *t*-test.

Table 2. Comparing among control group & patients groups concerning WBC, Hb and PLT.

	Control group	Studied cases group	Exam value	*P* value	Sig.
	Number = 20	Number = 30			
WBC					
Median (IQR)	6.8 (5.55–7.95)	12.05 (4.9–85)	−2.099	0.036	S
Range	3.5–10.6	0.3–332.9			
HB					
Mean ± SD	13.95 ± 1.55	9.83 ± 1.88	8.129	0.000	HS
Range	10.7–16	6.4–13			
PLT					
Median (IQR)	220 (176–252.5)	48 (33–267)	−2.386	0.017	S
Range	150–411	8–741			

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: highly significant.

Table 3. Comparing among control group & patients groups regarding protein C, protein S & antithrombin 3.

	Control group	Studied cases group	Test value	*P* value	Sig.
	Number = 20	Number = 30			
Protien C					
Mean ± SD	105.58 ± 22.55	73.30 ± 11.75	6.628	0.000	HS
Range	74.9–140	24.4–86.7			
Protein S					
Median (IQR)	112 (93.3–121.5)	41.45 (21.3–69.9)	−5.447	0.000	HS
Range	63–135	1.36–107			
Antithrombin 3					
Median (IQR)	95.05 (89.75–101.9)	53.55 (18.9–85.1)	−4.070	0.000	HS
Range	82.4–128	8.86–118			

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: highly significant.

3. Results

Group 1 (patient group):included (30) patient with acute lymphocytic leukemia (early diagnosed from 2 weeks) their age ranged from 2 to 81 year with a mean value 33.77 ± 21.21, they were 10 female and 20 male with a male female ratio 2:1. Group 2 (control group): included (20) patient apparently healthy, there age range from 19 to 67 year with a mean value 34.65 ± 12.55, they were 4 female and 16 male with a male female ratio 4:1. Table 1.

There was significant rise in median of total leucocytic count in patient group as compared with

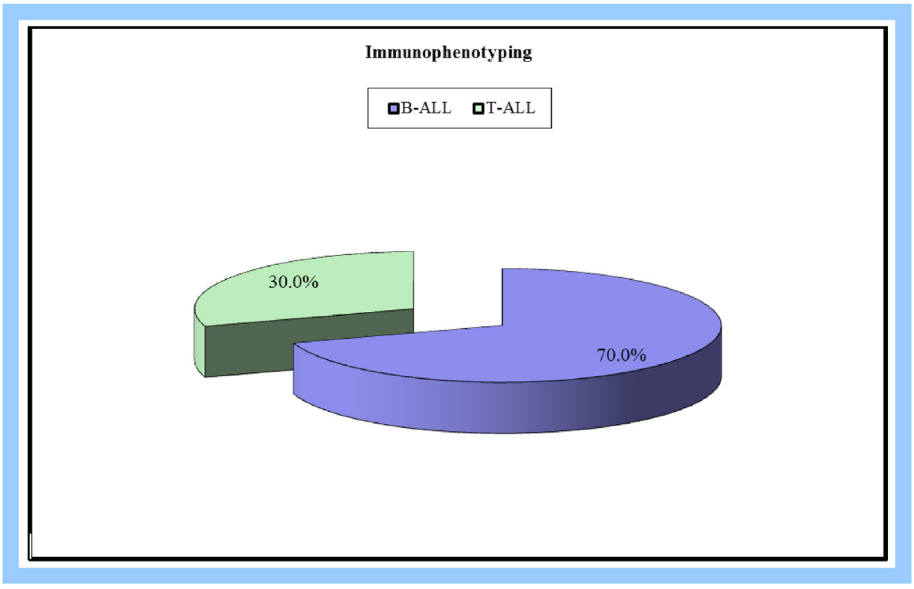

Fig. 1. Descriptive data of immunophenotyping.

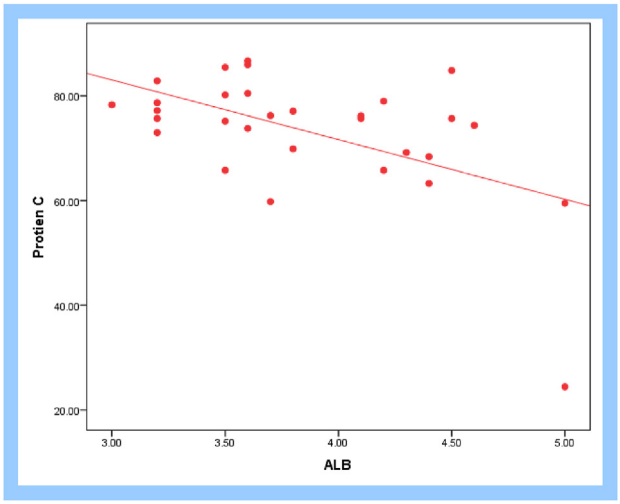

Fig. 2. Correlation between protein C and Albumin.

control group. This study showed that there is greatly important reduction in mean Hb level in patient group as compared to control group. There was important decrease in median value of platelets count in patient group as compared to control group. Table 2.

Mean values of activity levels of anticoagulant proteins (Protein C%) are significantly reduced in studied case group as compared to control group. median values of activity levels of anticoagulant proteins (Protein S, AT III (Anti thrombin III)%) are significantly reduced in studied case group as compared to control group (Table 3).

In this study, immunophenotyping of patients showed that 70% of patient were B-ALL and 30% T-ALL. In this study, immunophenotyping of patients showed that 70% of patient was B-ALL and 30% T-ALL (Fig. 1).

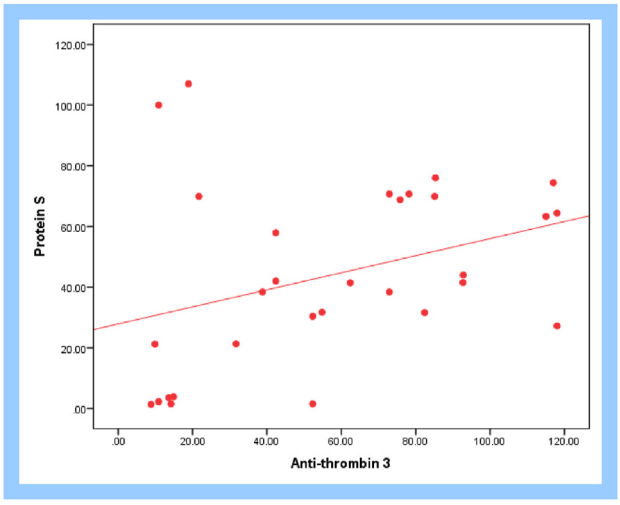

Fig. 3. Correlation between AT III (Anti thrombin III) & protein S.

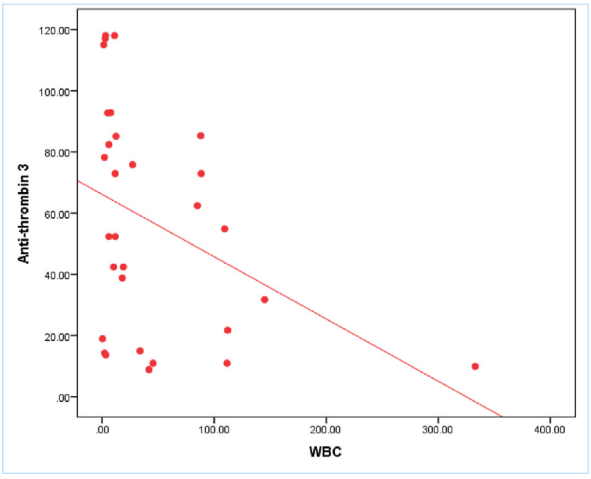

Fig. 4. Correlation between AT III (Anti thrombin III) & TLC.

There was statistically negative correlation among protein C & Albumin (Fig. 2). There was a positive correlation between AT III (Anti thrombin III) & protein S (Fig. 3). There was negative correlation among AT III (Anti thrombin III) & TLC (Fig. 4), Table 4.

This research exposed statistically no significant correlation among plasma activity levels of

Table 4. Relationship among plasma activity levels of anticoagulant (Protein C%) and clinical parameter of patients.

	Protein C		Test value	*P* value	Sig.
	Mean ± SD	Range			
Sex					
Female	74.56 ± 9.94	59.50–86.70	0.409	0.686	NS
Male	72.67 ± 12.75	24.40–84.90			
Immunopheno typing					
B-ALL	72.59 ± 12.96	24.40–86.00	−0.503	0.619	NS
T-ALL	74.97 ± 8.70	59.80–86.70			
Fever					
No	69.45 ± 16.43	24.40–86.00	−1.498	0.145	NS
Yes	75.87 ± 6.57	59.50–86.70			
Purpra					
No	71.13 ± 14.17	24.40–86.70	−1.012	0.320	NS
Yes	75.47 ± 8.66	59.50–86.00			
Pallor					
No	73.59 ± 8.39	59.80–84.90	0.072	0.943	NS
Yes	73.22 ± 12.75	24.40–86.70			
Lymph node					
No	75.86 ± 5.39	65.80–84.90	0.839	0.408	NS
Yes	72.02 ± 13.84	24.40–86.70			
Hepatomegaly					
No	72.68 ± 12.99	24.40–86.00	−0.436	0.666	NS
Yes	74.75 ± 8.66	59.80–86.70			
Splenomegaly					
No	72.72 ± 13.49	24.40–85.50	−0.350	0.729	NS
Yes	74.30 ± 8.42	59.80–86.70			

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: highly significant.

Table 5. Relationship among plasma activity levels of anticoagulant (Protein S %) and clinical parameter of patients.

	Protein S		Test value	*P* value	Sig.
	Median (IQR)	Range			
Sex					
Female	35.05 (21.20–70.70)	1.36–100.00	−0.660	0.509	NS
Male	43.00 (25.85–69.35)	1.53–107.00			
Immunophenotyping					
B-ALL	38.40 (21.30–68.80)	1.36–107.00	−0.543	0.587	NS
T-ALL	63.30 (30.40–69.90)	2.25–70.70			
Fever					
No	36.55 (24.25–50.95)	3.57–100.00	−0.678	0.498	NS
Yes	52.65 (3.86–70.70)	1.36–107.00			
purpra					
No	44.00 (21.20–68.80)	1.53–107.00	−0.353	0.724	NS
Yes	38.40 (21.30–69.90)	1.36–76.00			
pallor					
No	42.00 (30.40–64.40)	3.57–69.90	−0.049	0.961	NS
Yes	41.40 (21.20–70.70)	1.36–107.00			
lymph node					
No	32.80 (21.20–44.00)	1.53–74.40	−1.232	0.218	NS
Yes	49.95 (31.00–70.30)	1.36–107.00			
Hepatomegaly					
No	41.40 (21.20–64.40)	1.36–107.00	−0.679	0.497	NS
Yes	57.90 (30.40–69.90)	3.57–76.00			
Splenomegaly					
No	41.40 (3.86–70.70)	1.36–107.00	−0.344	0.731	NS
Yes	57.90 (30.40–69.90)	2.25–70.70			

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: highly significant.

Table 6. Relationship among plasma activity levels of anticoagulant (ATIII % (Antithrombin III) and clinical parameter of patients.

	Antithrombin 3		Test value	*P* value	Sig.
	Median (IQR)	Range			
Sex					
Female	46.80 (10.90–72.90)	8.86–118.00	−1.343	0.179	NS
Male	57.35 (26.70–89.00)	13.60–118.00			
Immunopheno typing					
B-ALL	54.80 (18.90–82.40)	8.86–118.00	−0.136	0.892	NS
T-ALL	52.30 (21.70–85.10)	10.90–118.00			
Fever					
No	53.55 (22.65–84.25)	9.89–118.00	−0.212	0.832	NS
Yes	62.60 (18.90–85.10)	8.86–118.00			
purpra					
No	72.90 (14.20–92.70)	9.89–118.00	−0.166	0.868	NS
Yes	52.30 (21.70–85.10)	8.86–118.00			
pallor					
No	82.40 (42.40–115.00)	13.60–118.00	−1.227	0.220	NS
Yes	52.30 (14.90–78.20)	8.86–118.00			
lymph node					
No	67.65 (14.20–92.80)	9.89–118.00	−0.308	0.758	NS
Yes	52.30 (20.30–83.75)	8.86–118.00			
Hepatomegaly					
No	52.30 (14.90–78.20)	8.86–118.00	−0.838	0.402	NS
Yes	72.90 (42.40–85.10)	13.60–118.00			
Splenomegaly					
No	42.40 (14.20–78.20)	8.86–117.00	−1.486	0.137	NS
Yes	72.90 (42.40–115.00)	10.90–118.00			

P value > 0.05: Non significant; *P* value < 0.05: Significant; *P* value < 0.01: highly significant.

anticoagulant (Protein C%) & clinical parameter of patients (Table 5).

This study revealed statistically no significant correlation among plasma activity levels of anticoagulant (Protein S%) & clinical parameter of patients (Table 6).

This research revealed statistically no significant relationship among plasma activity levels of anticoagulant (AT III% (Anti thrombin III) and clinical parameter of patients.

4. Discussion

Acute lymphoblastic leukemia (ALL) creates in single B- or T-lymphocyte proginitor. Proliferation & accumulation of blast cells in marrow finding in suppression of hematopoiesis & there after the presence of anemia, thrombocytopenia, and neutropenia.[7]

The occurrence of various coagulation abnormalities, i.e. a hypercoagulability state, in acute leukemia is a well-established phenomenon with hemorrhage and thrombosis as the most common hemostatic disorder.[8]

Protein C is vitamin k-dependent plasma serine protease zymogen that up on activation by thrombin-thrombomodulin complex down regulates clotting cascade by the feedback loop inhibition mechanism.[9]

Protein S is vitamin k-dependent anticoagulant protein. The main function of protein S is as cofactor to facilitate action of activated protein C on its substrates, activated factor V & activated factor VIII(F VIII a).[10]

Antithrombin III is glycoprotein formed by liver, member of family of serine protease inhibitor. It is main physiological anticoagulant that neutralizes thrombin & factors X a & XI a irreversibly by making complexes in the reactions accelerated by heparin or by heparin sulphate endothelial surface.[6]

Aim of research is to evaluate role of plasma activity levels of anticoagulant proteins (protein C, S & Anti thrombin III) in studied cases with acute lymphocytic leukemia.

This study was carried out on (30) patient with acute lymphoblastic leukemia (at early diagnosis) and (20) apparently healthy controls, the patients were selected from those admitted to hematology unit of El Hussin or Said galal Hospital. Informed consent was got from all subjects patients prior to their enrollment at this research.

This study reported that the most clinical symptoms of leukemia were pallor (76.7%), lymphadenopathy (66.7%), fever (60%), purpura (50%), splenomegaly (36.7%) and hepatomegaly (30%).

Other study reported that common symptoms were fever sixty percent of time, splenomegaly sixty three percent of time, lymphadenopathy fifty seven percent of time, pallor forty eight percent of time, & purpura thirty percent of time.[11]

Hepatomegaly, lymphadenopathy is due to infiltration of live, spleen and lymph nodes by malignant cells.[12] Also **Bothale *et al.***[13] found that infiltration of lymph nodes by leukemic cells can happen at any phase of disease. Extra medullary hematopoiesis happens when function of bone marrow is insufficient or destroyed.

In the current work, there was an important rise in median of total leucocytic count in patient group as compared with control group and this was in agreement with **Obi *et al.***[14] who described that uncontrolled proliferation of the blast cells in blood and bone marrow.

As regard Hemoglobin levels, this study showed that there was greatly important decrease in mean Hb level in patient group as compared to control group. This is in agreement with **Pui,**[15] who stated that ALL patients have anemia with Hemoglobin less than 10 g/dl. **Li** et al.[16] explained anemia due to a direct result of the diffuse and heavy bone marrow infiltration by lymphoblasts causing decrease in RBCS formation.

In present research, there is an important decrease in median value of platelets count in patient group as compared to control group & this agreed with **Ismail &Hamed,**[17] who stated that ALL patients had significant reduction of platelet count. These results were in constant also with **Brillantino *et al.***[18] who explained that reduced number of platelet count in ALL patients is usually the result of bone marrow infiltration with leukemic blasts causing decreased production of platelets and decrease survival of platelet.

As regard liver function, there were no significant variations in (AST, ALT, serum Albumin) in patient group as compared to control group & this study is in agreement with **Ismail & Hamed,**[17] who stated that there were no significant variations in (AST, ALT, serum Albumin) in patient group as compared to control group & this reflects normal liver function.

As regard kidney function, there was no significant variations in (serum urea level & serum creatinine level) in patient group as compared to control group & this in agreement with **Ismail & Hamed.**[17]

In the present work, the mean values of activity levels of anticoagulant proteins (Protein C percent, Protein S & AT III (Anti thrombin III)%) were highly significant reduced in studied case group as compared to control group.

This results in constant with **Ismail & Hamed,**[17] who found that there are highly important reduction in activity levels of anticoagulant protein (Protein C percent, Protein S & ATIII (Anti thrombin III) percent) in patient group as compared to control group at duration of diagnosis, might possibly be due to consumption of these proteins because of subclinical coagulation activation, due to increase tissue factor release by ALL cells and depression of thrombomodulin.

Additionally, **Osei-OWusu *et al.***[19] stated that significant reduction in natural anticoagulant (Protein C percent, Protein S & AT III (Anti thrombin III) percent) in acute leukemia studied cases might suggests hypercoagulable state in patient group.

Also the previous results were in agreement **Ito *et al.***[20] who stated that low level of natural anticoagulant protiens (Protein C percent, Protein S & AT III (Anti thrombin III percent) in acute leukemia studied cases have been observed, are proposed to be associated with modified pattern of hepatic protein synthesis to creation of acute phase proteins.

Immunophenotyping represents a corner stone in establishing the diagnosis and assesment of outcome in acute leukemia patients. In this study, immunophenotyping of patients showed that 70% of patients were B-ALL and 30% T-ALL and this is in agreement with **De Bie *et al.***[7] who found that the phenotyping was towards a relatively higher incidence of Precursor B- lineage. AN Egyptian study done by **Hagag *et al.***[21] found that 70% of patients were B-ALL and 30% were T-ALL.

This research revealed statistically no important relationship among plasma activity levels of anticoagulant protiens (Protein C percent, Protein S & AT III percent) & (clinical parameter of patients, Hb, AST, ALT, Urea & creatinine).

While there was statistically negative relationship among protein C & Albumin, there was a negative correlation between.

ATIII (Anti thrombin III) & TLC and there is a positive correlation between AT III (Anti thrombin III) & protein S.

This finding are in consistent with **Ismail & Hamed,**[17] who suggested that these correlations between plasma activity levels of anticoagulant proteins (Protein C percent, Protein S & AT III percent) & other laboratory parameters denote a hypercoagulability state in ALL patients.

5. Conclusion

Plasma activity levels of Protein C, Protein S & Anti thrombin III were significant decreased in patients with acute lymphoblastic leukemia (at early

diagnosis). Plasma activity levels of Protein C, Protein S & Anti thrombin III may be consider as a biomarker for hypercoaguable state in studied cases with Acute lymphoblastic leukemia (at early diagnosis).

Conflict of interest

None declared.

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