https://doi.org/10.15218/zjms.2023.019

Early hemostatic derangements in patients with de novo acute leukemia: A single center experience

Received: 07/07/2022 Accepted: 25/08/2022

Sarah Laith Alnuaimy [1]* Rawand P. Shamoon [2]

Abstract

Background and objective: Bleeding and thrombosis are major causes of morbidity and mortality in patients with acute leukemia (AL); they are attributed to hemostatic derangement and coagulation defects that are associated with leukemia. There is a paucity of information regarding coagulopathy in AL patients in our locality; this study, therefore, was employed to evaluate hemostatic parameters in patients with AL at the time of presentation.

Methods: This prospective cross-sectional study included 84 newly diagnosed patients with AL. The study was carried out at Nanakali hemato-oncology center from September 2021 to May 2022. Patients were assessed for coagulation parameters including prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen level (FBG), D-dimer (D-Di), antithrombin (AT), protein C (PC), and protein S (PS).

Results: The median age of the studied patients was 26 years with a male to female ratio of 1.1:1. Acute myeloid leukemia (AML) patients constitutes 51.2% (43 patients), and the remaining 41 (48.8%) patients had acute lymphoblastic leukemia (ALL). PT was significantly prolonged, D-Di was significantly higher and AT, and PC were significantly decreased in AML compared to control groups. Only D-Di level was significantly higher in ALL compared to control groups. Bleeding manifestations were encountered in 40 (47.6%) patients with a higher incidence among the AML group (28 patients, 70%). Thrombosis occurred in 2 (2.4%) patients.

Conclusion: Defects of coagulation were common in AL. Hemostatic derangement and bleeding at the time of presentation were more noticeable in patients with AML.

Keywords: Bleeding; Thrombosis; Hemostatic derangement.

Introduction

AL is a diverse entity of blood malignancies that results from the accumulation of immature precursor cells in the bone marrow and the peripheral blood. AML and ALL are the main types of AL.[1] Adults are more likely to get AML, while children are more likely to develop ALL.[2]The incidence of leukemia in Iraq has increased from 3.24/100,000 in 2000 to 4.37/100,000 in 2016.[3]

Advances in the management of various types of AL have turned these lethal malignancies into potentially curable ones. However, both thrombosis and hemorrhage, as overt manifestations of underlying coagulopathy, continue to cause considerable deaths in patients with AL.[4]Coagulopathy is quite common in AL, and its pathogenesis is complex and incompletely understood. Tissue factor molecules are over-expressed on the surface of leukemic cells in all types of AL. Production of cancer procoagulant, a cysteine protease that directly activates factor X, by the leukemic cells is universal in leukemias. Other unique mechanisms for coagulopathy include the expression of

[1] Unit of Hematopathology, Nanakali Hemato-oncology Hospital, Erbil, Iraq.
[2] Department of Basic Sciences, College of Medicine, Hawler Medical University, Erbil, Iraq.
Correspondence: dr_sara812@yahoo.com

https://doi.org/10.15218/zjms.2023.019

annexin II, a cell receptor that activates tissue plasminogen activator. Levels of urokinase plasminogen activator have also been found to be increased. Decreased levels of plasminogen activator inhibitor-1and thrombin activatable fibrinolytic inhibitor may explain the hyperfibrinolysis that is associated with some types of AL.[5,6]

Hemorrhage predominates in acute promyelocytic leukemia (APL) while also thrombosis may occur, though thrombosis is more common in patients with ALL. Alterations in the level of naturally occurring anticoagulants like PC, PS, and AT have also been studied as factors that may increase the thrombotic tendency especially, in patients with ALL.[4,7]

To the best of our knowledge, no studies have addressed the issues of coagulopathy in patients with AL at the time of presentation in our locality. This study, therefore, was carried out to evaluate the coagulation markers in patients with different AL subtypes, and to detect the incidence of bleeding and thrombotic events at presentation, as some of these patients may require early intervention with supportive or specific therapies that might help in reducing morbidity and mortality associated with these complications.

Methods

This prospective cross-sectional comparative study was carried out from September 2021 to May 2022 at Nanakali hemato-oncology center, Erbil, Iraqi Kurdistan. A total of 84 consecutive newly diagnosed patients with de novo AL of all ages were enrolled in this study, together with 50 apparently healthy control subjects after obtaining written consent. The diagnosis of AL was based on clinical and morphological findings of peripheral blood, bone marrow (BM) aspirates and biopsies. Confirmation and classification of AL were done based on the immunophenotypic characteristics using BD flowcytometry (BD FACSymphony™ A1 Cell Analyzer, New Jersey, USA). Cases with bleeding tendency or thrombophilia, those with organ failure, patients on anticoagulants, patients who received supportive or definite therapy, and pregnant ladies were excluded from this study.

Patients were fully examined, and comprehensive clinical and lab data were recorded. Bleedings were graded as per the WHO grading system.[8] Early death was defined as death within 30 days of diagnosis. PT, APTT, and FBG were performed using Stagocoagulometer (STA Compact, France). Plasma D-Di level and AT were measured as per the manufacturer's kits and instructions (Roche, Hitachi Cobas 6000 analyzer). PC and PS were performed by ELISA based method using (Aesku Diagnostics GmbH, Wendelsheim, Germany).

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 25). Numerical variables were expressed as median (and range) and mean (SD). Comparison between two groups was done by Mann-Whitney U test and between more than two groups by Kruskal-Wallis test with post hoc Bonferroni adjustment. Categorical variables were expressed as frequencies (percentages). Chi-square test and Fisher's exact test were used to compare categorical variables. A *P*-value of ≤0.05 was considered statistically significant.

Results

Eighty-four patients with de novo AL were included in this study, of whom 44 (52.4%) were male. The control group consisted of 50 healthy individuals, age and gender-matched, apparently healthy individuals of whom 29 (58%) were male. The mean (SD) age of the patients and controls were 30.68 (23.4) and 31 (19.5) years, respectively. Details of the demographic data are shown in Table 1.

Table 2 shows the hematologic and coagulation parameters of the AML and ALL patients.

https://doi.org/10.15218/zjms.2023.019

Table 1 Characteristics of patients and control groups

Variables		Patients	Control	*P*
Age (years)	Mean (SD)	30.68 (23.4)	31.54 (19.5)	0.749*
	Median (Range)	26 (0.1-81)	30 (0.9-72)	
BMI (Kg/m^2)	Mean (SD)	23.82 (5.48)	23.21 (3.95)	0.511*
	Median (Range)	25.5 (14-41)	25 (15.2-27)	
Gender	Male No. (%)	44 (52.4)	29 (58)	0.528**
	Female No. (%)	40 (47.6)	21 (42)	

* By Mann-Whitney U Test. ** By Chi-square test.

Table 2 Lab parameters of AML and ALL patients

Lab parameters	AML		ALL	
	Mean (SD)	**Median (range)**	**Mean (SD)**	**Median (range)**
Hematological parameters				
Hb (g/dl)	8.16 (1.8)	7.8 (4.9-13.2)	9.23 (2.30)	8.9 (3.7-15.1)
WBC (×10^9/L)	52.8 (78.8)	14.3 (1.6-360)	41.2 (73.6)	16.8 (0.4-376)
Platelet (×10^9/L)	58.7 (54.8)	42.0 (6-268)	73.3 (81.8)	53.0 (23-98)
Blast in PB (%)	46.6 (31.8)	48.0 (0-98)	53.0 (31.5)	60.0 (0-94)
Blast in BM (%)	67.2 (22.8)	80.0 (20-96)	82.7 (13.7)	90.0 (23-98)
ESR (mm/hr)	70.16 (35.5)	56.0 (20-150)	58.41 (33.3)	50.0 (3-155)
Coagulation markers				
PT (sec.)	18.14 (4.43)	17.8 (10.1-33)	14.12 (2.37)	13.9 (10.4-21.9)
APTT (sec.)	32.98 (8.30)	30.0 (20.9-54.0)	30.77 (5.33)	30 (21.9-44.4)
FBG (g/l)	2.44 (1.47)	2.14 (0.40-7.20)	2.63 (1.21)	2.44 (0.50-5.96)
D-Di (µg/ml)	11.15 (12.5)	7.4 (0.16-59.82)	6.96 (12.5)	3.38 (0.19-73.0)
PC (%)	75.43 (34.47)	68.0 (14.5-162)	123.3 (60.1)	119.0 (24.0-272)
PS (%)	75.15 (29.93)	73.7 (19.1-146.1)	81.86 (35.1)	70.0 (20.1-173)
AT (%)	86.92 (20.65)	90.0 (20.0-130.0)	106.2 (21.8)	110.0 (59-147.4)
Biochemical parameters				
CRP (mg/l)	30.89 (19.5)	32.0 (2.84-78)	21.68 (23.98)	10.0 (1.40-102)
S.LDH (U/L)	964.3 (823)	716 (207-4781)	1547 (2867)	746 (212-15207)

https://doi.org/10.15218/zjms.2023.019

Table 3 shows the hemostatic parameters in AL patients. The predominant abnormality was thrombocytopenia which was encountered in 76 (90.5%) patients, followed by raised D-Di level that found in 73 (86.9%) patients, and prolonged APTT and hypofibrinogenemia were the least detected in 18 (21.4%) patients each.

Table 3 Hemostatic parameters in AL

Parameters	AML		ALL		Total
	APL	Non-APL	B-ALL	T-ALL	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Platelet count ($\times 10^9$/L)					
Normal (≥150)	0 (0.0)	4 (11.1)	4 (87.5)	0 (0.0)	8 (9.5)
Decreased (150)	7 (100.0)	32 (88.9)	28 (12.5)	9 (100.0)	76 (90.5)
PT (sec)					
Normal (≤14)	0 (0.0)	7 (19.4)	20 (62.5)	3 (33.3)	30 (35.7)
Prolonged (>14)	7 (100.0)	29 (80.6)	12 (37.5)	6 (66.7)	54 (64.3)
APTT (sec)					
Normal (≤36)	5 (71.4)	26 (72.2)	28 (87.5)	7 (77.8)	66 (78.6)
Prolonged (>36)	2 (28.6)	10 (27.8)	4 (12.5)	2 (22.2)	18 (21.4)
FBG (g/l)					
Normal (≥1.5)	2 (28.6)	30 (83.3)	28 (87.5)	6 (66.7)	66 (78.6)
Decreased (<1.5)	5 (71.4)	6 (16.7)	4 (12.5)	3 (33.3)	18 (21.4)
D-Di (µg/ml)					
Normal (<0.5)	0 (0.0)	3 (8.3)	7 (21.9)	1 (11.1)	11 (13.1)
Increased (≥0.5)	7 (100)	33 (91.7)	25 (78.1)	8 (88.9)	73 (86.9)
PC (%)					
Normal (≥70)	4 (57.1)	16 (44.4)	28 (87.5)	7 (77.8)	55 (65.5)
Decreased <70	3 (42.9)	20 (55.6)	4 (12.5)	2 (22.2)	29 (34.5)
PS (%)					
Normal (≥60)	6 (85.7)	22 (38.9)	27 (84.4)	5 (55.6)	60 (71.4)
Decreased (<60)	1 (14.3)	14 (61.1)	5 (15.6)	4 (44.4)	24 (28.6)
AT (%)					
Normal (≥80)	7 (100.0)	21 (58.3)	25 (78.1)	9 (100.0)	62 (73.8)
Decreased (<80)	0 (0.0)	15 (41.7)	7 (21.9)	0 (0.0)	22 (26.2)
Total	7 (100.0)	36 (100.0)	32 (100.0)	9 (100.0)	84 (100.0)

https://doi.org/10.15218/zjms.2023.019

Table 4 shows the comparison of the coagulation parameters between the AML, ALL patients, and the control groups. There was a statistically significant difference in PT between AML and ALL and the AML and control groups. The D-Di was significantly higher in the AML and ALL patients compared to the control group. PC and AT levels were significantly lower in the AML patients compared to the ALL and control groups (P = 0.001); however, PC and AT levels were not significantly different when the ALL group was compared to the control group. PS did not show a significant difference among the three groups.

Table 4 Comparison of coagulation markers between AML, ALL patients, and controls

	Group	Mean	SD	p (KW)	Groups	p (post hoc)
PT (sec)	A) AML	18.14	4.43		A x B	< 0.001
	B) ALL	14.12	2.37		A x C	< 0.001
	C) Control	13.36	1.03	< 0.001	B x C	0.738
APTT (sec)	A) AML	32.98	8.30		NA	NA
	B) ALL	30.77	5.33			
	C) Control	31.82	2.69	0.215		
FBG (g/l)	A) AML	2.44	1.47		NA	NA
	B) ALL	2.63	1.21			
	C) Control	2.50	0.84	0.412		
D-Di (µg/ml)	A) AML	11.15	12.49		A x B	0.266
	B) ALL	6.98	12.63		A x C	< 0.001
	C) Control	0.20	0.15	< 0.001	B x C	< 0.001
PC (%)	A) AML	75.43	34.47		A x B	< 0.001
	B) ALL	123.34	60.12		A x C	< 0.001
	C) Control	120.9	41.5	< 0.001	B x C	1.000
PS (%)	A) AML	75.15	29.93		NA	NA
	B) ALL	81.86	35.07			
	C) Control	79.4	15.55	0.463		
AT (%)	A) AML	86.92	20.65		A x B	< 0.001
	B) ALL	106.02	21.83		A x C	< 0.001
	C) Control	108.85	13.18	< 0.001	B x C	1.000

NA: Multiple comparisons are not performed by the SPSS because the overall test does not show significant differences across samples. KW: Kruskal-Wallis H test.

https://doi.org/10.15218/zjms.2023.019

Table 5 demonstrates the comparison of the coagulation markers between leukemic subtypes, APL and non-APL AML patients and B-ALL and T-ALL patients. FBG was significantly lower, and PS and AT were significantly higher in APL patients compared to non-APL AMLs patients. The comparison between B-ALL and T-ALL revealed that only PT and INR differ significantly between the two groups, the remaining parameters did not show any statistically significant differences.

Bleeding events occurred in 40 (47.6%) patients, 28 had AML and 12 had ALL. Concerning grading, grade 4 was recorded only in APL patients, while grade 3 was observed in APL and non-APL patients. Grade 2 occurred in all the subtypes as it is illustrated in Figure 1.

Two AL cases (2.4%) had thrombotic events at the time of presentation. The first case was a non-APL case with deep vein thrombosis and pulmonary embolism, the second case was a B-ALL with deep vein thrombosis. Both cases had normal PT and APTT with thrombocytopenia and elevated D-Di. They had normal PC, PS, and AT levels. Thrombophilia molecular study showed 3 mutations, MTR 2756, PAI 4G/5G, and Beta-Fibrinogen 455 G>A in the first case and 2 mutations, Angiotensin-Converting Enzyme (ACE) 287 bp insertion/deletion (I/D), Human Platelet Antigen 1 (HPA 1; GP 111a) L33P (1a/1b) in the second case.

Table 5 Comparison of coagulation markers between APL and non-APL patients within AML group and between B-ALL and T-ALL patients within ALL group

Markers	AML			ALL		
	APL	Non-APL	P*	B-ALL	T-ALL	P*
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
PT (sec)	20.99 (6.3)	17.59 (3.8)	0.130	13.75 (2.2)	15.46 (2.7)	0.049
APTT (sec)	34.63 (11.8)	32.66 (7.6)	0.948	30.96 (5.3)	30.09 (5.6)	0.741
FBG (g/l)	1.88 (2.0)	2.55 (1.4)	0.018	2.61 (1.1)	2.73 (1.6)	0.975
D-Di (µg/ml)	9.47 (2.7)	11.47 (13.6)	0.340	7.67 (14.2)	4.53 (3.0)	0.659
PC (%)	74.69 (23.4)	75.57 (36.5)	0.717	125.95 (62.3)	114.06 (53.9)	0.862
PS (%)	102.46 (27.3)	69.84 (27.7)	0.012	86.89 (35.2)	63.96 (29.6)	0.108
AT (%)	102.10 (11.2)	83.97 (20.9)	0.012	105.96 (23.4)	106.21 (15.9)	0.682

* By Mann-Whitney U Test.

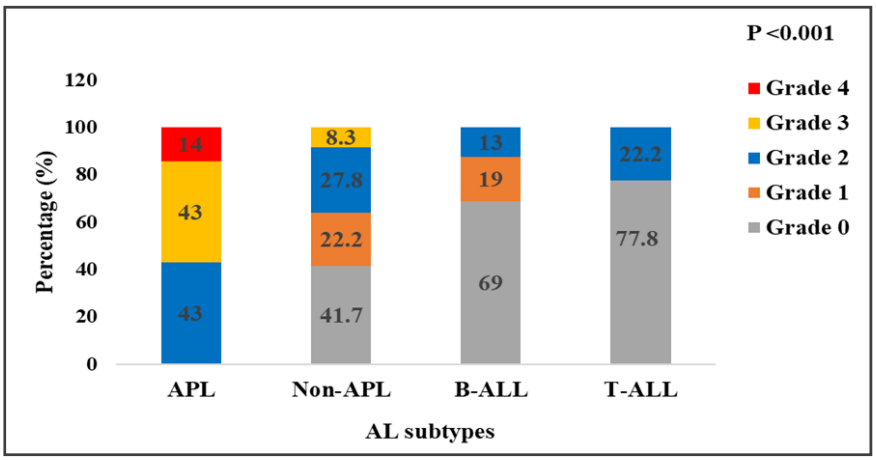

Figure 1 Grading of bleeding among subtypes of AL

https://doi.org/10.15218/zjms.2023.019

Discussion

Despite advances in AL treatment that have enhanced survival rates, AL remains a grave disease. The rate of early mortality is still high and unchanged; this is mostly owing to early hemorrhage and, to a lesser extent, thrombosis, which characterize this disease. These, in turn, represent the distinct and complex underlying coagulopathy that manifests early in the course of AL.[4] This study investigated several coagulation parameters in AL patients at early presentation prior to starting specific or supportive therapy.

Our study cohort consisted of 84 patients with de novo AL and a comparable group of 50 unrelated apparently healthy, age and gender matched, control subjects. In the current study, the median patients age was 26 years, with a range of 0.1 to 81 years, which was lower than what has been reported by other studies.[9,10] Approximately two-thirds of the cases were > 15 years. Males were slightly more than females, and this was comparable to the local studies.[10-12] This male predominance appears to be a universal character across the five continents.[13] In our cohort, ALL was almost as common as AML, and this goes with some international and local studies.[14,15] Non-APL AML was the commonest subtype (42.9%). APL, which is a specific subtype of AML, constituted about 8% of all patients. In addition, B-ALL and T-ALL constituted 38% and 10% of the patients, respectively. Similar proportions were reported in a cohort of 282 Iraqis with ALL where B-ALL predominated.[16]

We detected variable derangements of coagulation markers in our AL patients at the time of presentation. The main findings go in line with those found by many studies worldwide. PT was prolonged in 54 (64.3%) patients, D-Di was raised in 73 (86.9%), APTT was prolonged and FBG was reduced in 18 patients (21.4%) each. Thrombocytopenia (<150 x10^9/L) was found in 76 (90.5%) patients.

The pathophysiology of hemostatic derangements in AL is complex and multifactorial. The proteins expressed by the leukemic cells acting as procoagulants, the cytokines production by them, the endothelial disruption, the protease activity, and primary and secondary fibrinolysis in specific subtypes of AL all together play variable roles.[4]The APTT was prolonged and FBG decreased relatively in a few proportions of patients; however, these findings were due to consumptions of clotting factors in these patients but the fact that should be emphasized here is that FVIII and FBG are positive acute phase reactants and they often require more time in AL patients before they begin to decline.[17] Different studies reported variable rates of derangement in coagulation and fibrinolytic markers and platelet counts. The similarities and disparities in these results may be explained by the differences in the characteristics of the studied cohorts including leukemic subtype, age, and gender.[18,19]

Nearly one third of the current AL patients had reduced levels of natural coagulation inhibitors; PC in 34.5%, PS in 28.6%, and AT in 26.2% of the patients. The reduction in PC and PS could be attributed to the cytokine release in AL and the systemic inflammation which leads to the down regulation of thrombomodulin and consequently lowering the PC and PS.[20]

We found significant prolongation of PT in AML patients compared to ALL patients; however, D-Di levels did not differ significantly in the two groups. PC levels were significantly lower in AML patients compared to ALL patients and controls. AML cases had maximum derangements in hemostatic marker, this is quite similar to other studies.[21] These findings support the notion that coagulopathy in AL is somewhat type and subtype dependent. Within the AML group, we found significant hypofibrinogenemia in APL patients compared to non-APLAML (P = 0.018). Non-APL cases had significantly higher D-Di levels and lower AT levels; these

findings were in agreement with other studies.[22]

In the enrolled AL patients, bleeding occurred in 40 (47.6%) patients, of whom more than two-thirds had AML (28 patients, 70%). The distribution of bleeding among AL subtypes revealed that highest proportion of bleeding diathesis occurred in non-APL (21 patients, 52.5%), followed by B-ALL (10 patients, 25%). Local studies reported similar bleeding incidences in ALL.[23] Though, the incidence of bleeding in our AML cases was 65.1% which is higher than what was reported in a study done in Sulaymaniyah, other studies revealed lower incidences of bleeding.[10,24,25]

These variations may be due to the fact that most of the studies were retrospective and bleeding incidents might have not been appropriately recorded. However, the higher incidence of bleeding in AML compared to ALL is mostly due to the biological nature of myeloblasts expressing more fibrinolytic activity than lymphoblasts.[4]

In our AL patients, bleedings were predominantly of grades 1 and 2; bleedings of grades 3 and 4 were observed among AML cases with the latter only detected in APL patients and found in 14% of them. The incidence of bleeding in APL was 100%, this was dissimilar to a study conducted in China which reported bleeding events in 46.6% of patients.[8] Kim et al[26]and Chang et al[27] found much lower bleeding rates among their cohorts, 26% and 22.4%, respectively. This could be attributed to the fact that our study included relatively fewer cases of APL than other studies that particularly studied the APL subtype; therefore, the findings of our study cannot draw a definite conclusion.

In the current cohort, only two AL patients (2.4%) have had venous thrombosis at presentation. This rate keeps with the very wide range for thrombosis in AL reported in the literature ranging from 1.1-36.7% for ALL and 3.2-9.6% for AML. This wide variation in the incidence of venous thromboembolism has been explained by the variable diagnosis and treatment methods of thrombosis and by different studies.[28]

Conclusion

Coagulation aberrations are common in patients with AL at presentation, more prominently in AML. Bleeding manifestations were more common in AML patients, with significantly higher rates and severity among APL type. The rate of thrombosis was relatively low. Larger multicenter studies are required to better assess coagulopathy and bleeding in newly diagnosed AL.

Funding

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Okikiolu J, Dillon R, Raj K. Acute leukaemia. Medicine. 2021; 49(5):274–81. https://doi.org/10.1016/j.mpmed.2021.02.004.
2. Rose-Inman H, Kuehl D. Acuteleukemia. Hematol Oncol Clin North Am. 2017; 31(6):1011–28. https://doi.org/10.1016/j.hoc.2017.08.006.
3. Hussain AMA, Lafta RK. Cancer trends in Iraq 2000–2016. Oman Med J 2021;36(1):e219. https://doi.org/10.5001%2Fomj.2021.18.
4. Cate H, Leader A.Management of disseminated intravascular coagulation in acute leukemias. Hamostaseologie. 2021; 41(2):120–6. https://doi.org/10.1055/a-1393-8302.
5. Kwaan HC, Weiss I, Tallman MS. The role of abnormal hemostasis and fibrinolysis in morbidity and mortality of acute promyelocytic leukemia. Semin Thromb Hemost. 2019; 45(06):612–21. https://doi.org/10.1055/s-0039-1693478.
6. Lad D, Jain A, Varma S. Complications and management of coagulation disorders in leukemia patients. Blood Lymphat Cancer. 2017; 7:61–72. https://doi.org/10.2147/BLCTT.S125121.
7. Ismail MM, Hamed GM. Activity levels of natural anticoagulant proteins in childhood acute lymphoblastic leukemia: relation to thromboembolic complications and treatment. Blood Coagul Fibrinolysis. 2017; 28(1):1–7. https://doi.org/10.1097/MBC.0000000000000521
8. Chu T, Wang H, Lv X, Qi J, Tang Y, Fan Y, et al. Investigation of fibrinogen in early bleeding of patients with newly diagnosed acute promyelocytic leukemia. Platelets. 2021; 32(5): 677–83. https://doi.org/10.1080/09537104.2020.1799969.

9. Shahmarvand N, Oak JS, Cascio MJ, Alcasid M, Goodman E, Medeiros BC, et al. A study of disseminated intravascular coagulation in acute leukemia reveals markedly elevated D-dimer levels are a sensitive indicator of acute promyelocytic leukemia. Int J Lab Hematol. 2017; 39(4):375–83. https://doi.org/10.1111/ijlh.12636.
10. Tawfiq S, Yassin A, AlGetta H, Hassan K. Acute myeloblastic leukemia: important clinical and epidemiological facts from Hiwahospital in Sulaimaniyah, Iraq. Iraqi Journal of Hematology. 2019; 8:69. https://doi.org/10.4103/ijh.ijh_11_19.
11. Abuhelwa Z, Shaer QA, Taha S, Ayoub K, Amer R. Characteristics of de novo acute myeloid leukemia patients in Palestine: experience of An-Najah national university hospital. Asian Pac J Cancer Prev. 2017; 18(9):2459–64. https://doi.org/10.22034/APJCP.2017.18.9.2459.
12. Karim ZA, Khidhir KG, Ahmed RA, Hassan HA, Karim DO. Leukemia study in Sulaymaniyah province, Kurdistan, Iraq. Chin Med J (Engl). 2016; 129(2):244–5. https://doi.org/10.4103%2F0366-6999.173551.
13. Edgren G, Liang L, Adami HO, Chang ET. Enigmatic sex disparities in cancer incidence. Eur J Epidemiol. 2012; 27(3):187–96. https://doi.org/10.1007/s10654-011-9647-5.
14. Gómez-Almaguer D, Marcos-Ramírez ER, Montaño-Figueroa EH, Ruiz-Argüelles GJ, Best-Aguilera CR, López-Sánchez MDC, et al. Acuteleukemia characteristics are different around the world: the Mexican perspective. Clin Lymphoma Myeloma Leuk. 2017; 17(1):46–51. https://doi.org/10.1016/j.clml.2016.09.003.
15. Mjali A, Al-Shammari HHJ, Abbas NT, Azeez ZD, Abbas SK. Leukemia epidemiology in Karbala province of Iraq. Asian Pacific Journal of Cancer Care. 2019; 4(4):135–9. https://doi.org/10.31557/apjcc.2019.4.4.135-139.
16. Jalal SD, Al-Allawi NAS, Al Doski AAS. Immunophenotypic aberrancies in acute lymphoblastic leukemia from 282 Iraqi patients. Int J Lab Hematol. 2017; 39(6):625–32. https://doi.org/10.1111/ijlh.12716.
17. Favaloro EJ. Laboratory testing in disseminated intravascular coagulation. Semin Thromb Hemost. 2010; 36(4):458–67. https://doi.org/10.1055/s-0030-1254055.
18. Hu W, Wang X, Yang R. Evaluation of D-dimer and lactate dehydrogenaseplasma levels in patients with relapsed acute leukemia. Oncol Lett 2016; 12(1):591–6. https://doi.org/10.3892/ol.2016.4657.
19. Chowdhury MU, Begum M, Khan MR, Kabir AL, Islam S, Layla KN, et al. Disseminated intravascular coagulation at diagnosis in acute myeloblastic leukaemia. J Biosci Med. 2021; 9(10):124–34. https://doi.org/10.4236/jbm.2021.910011.
20. Choudhry A, DeLoughery TG. Bleeding and thrombosis in acute promyelocytic leukemia. Am J Hematol. 2012; 87(6):596–603. https://doi.org/10.1002/ajh.23158.
21. Franchini M, Di Minno MND, Coppola A. Disseminated intravascular coagulation in hematologic malignancies. Semin Thromb Hemost. 2010; 36(4):388–403. https://doi.org/10.1055/s-0032-1331154.
22. Lee HJ, Park HJ, Kim HW, Park SG. Comparison of laboratory characteristics between acute promyelocytic leukemia and other subtypes of acute myeloid leukemia with disseminated intravascular coagulation. Blood Res. 2013; 48(4):250–3. https://doi.org/10.5045/br.2013.48.4.250.
23. Shalal HH, Mahmood NS, Alchalabi MAQ. Clinical, hematological, and laboratory presentation of acute lymphoblastic leukemia of children in Diyala province/Eastern Iraq. Int J Res Med Sc. 2017; 5(10):4227–33. https://doi.org/10.18203/2320-6012.ijrms20174551.
24. Shahab F, Raziq F. Clinical presentations of acute leukemia. J Coll Physicians Surg Pak. 2014; 24(7):472–6.
25. Cvetković M, Mitrović M. Disseminated intravascular coagulopathy in non-promyelocytic acute myeloid leukemia: incidence, clinical and laboratory features and prognostic significance. Serbian Journal of the Medical Chamber. 2021; 2 (2):99–109. http://dx.doi.org/10.5937/smclk2-32467.
26. Kim DY, Lee JH, Lee JH, Kim SD, Lim SN, Choi Y, et al. Significance of fibrinogen, D-dimer, and LDH levels in predicting the risk of bleeding in patients with acute promyelocytic leukemia. Leuk Res. 2011; 35(2):152–8. https://doi.org/10.1016/j.leukres.2010.05.022.
27. Chang H, Kuo MC, Shih LY, Dunn P, Wang PN, Wu JH, et al. Clinical bleeding events and laboratory coagulation profiles in acute promyelocytic leukemia. Eur J Haematol. 2012; 88(4):321–8. https://doi.org/10.1111/j.1600-0609.2011.01747.x.
28. Libourel EJ, Klerk CPW, van Norden Y, de Maat MPM, Kruip MJ, Sonneveld P, et al. Disseminated intravascular coagulation at diagnosis is a strong predictor for thrombosis in acute myeloid leukemia. Blood. 2016; 128 (14):1854–61. https://doi.org/10.1182/blood-2016-02-701094.