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Coagulation aberrations in adult patients with acute leukemia: A single center experience

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Abstract

Background and objective: Acute leukemia (AL) patients are at high risk for bleeding and thrombotic events due to the disruption of the normal hemostatic system associated with this disease. As a result of the lack of data on coagulopathy in AL patients in our locality, we conducted this study to assess the hemostatic parameters in patients with newly diagnosed AL at the time of presentation.

Methods: This prospective cross-sectional study included 59 patients with de novo AL, along with 35healthy control subjects. The study was conducted at Nanakali Hemato-Oncology Center between September 2021 and May 2022. Coagulation markers, including prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen levels (FBG), D-dimer (D-Di), antithrombin (AT), protein C (PC), and protein S (PS) were measured for each patient and control.

Results: The median age of the patients was 41 years, with a male to female ratio of 1.1:1. Thirty-eight (64.4%) patients had acute myeloid leukemia (AML) and 21 (35.6%) patients had acute lymphoblastic leukemia (ALL). D-Dilevels were significantly raised in both AML and ALL compared to controls. PT was significantly higher, and PC and AT were significantly lower in AML compared to ALL or control groups. The Bleeding incidence in AML was significantly higher than in ALL (65.8% versus 23.8%). Thrombosis occurred in two (3.4%) patients.

Conclusion: Coagulation abnormalities were common in AL. The hemostatic derangement and bleeding at the time of presentation were more pronounced in patients with AML than in ALL.

Keywords: Acute leukemia; Bleeding; Hemostatic derangement.

Introduction

Acute leukemia (AL) is a heterogenous entity of hematological malignancies that results from the clonal expansion of immature precursor cells in the bone marrow and the peripheral blood. The two main types of AL are AML and ALL.[1]

The AML predominates in adults with a median age of 68 years, while ALL predominates in children with another peak after the age of 40.[2] Over the last two decades, there has been a general upward trend in the prevalence of AL all over the world. The global number for ALL cases increased from 49,100 in 1990 to 64,200 in 2017, while for the AML, from 63,800 in 1990 to 119,600 in 2017.[3]

Hemorrhage and thrombosis contribute considerably to morbidity and mortality in AL, which occur as a manifestation of underlying hemostatic derangement associated with this disease.[4] The pathogenesis of the coagulopathy is complex and not fully understood; however, the platelets which are responsible for the primary hemostasis are usually decreased in AL due to bone marrow failure and consumption, while the

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clotting pathways are disrupted by several factors such as the disease-related factors, including the properties of the leukemic cells and how they interact with the other host cells as they express specific proteins that interact with the hemostatic system including expression of tissue factors, cancer procoagulants, and microparticles which can trigger the coagulation cascade resulting in thrombin generation. On the other hand, another unique mechanism for coagulopathy is the enhanced fibrinolytic activity due to increased expression of annexin II, which activates the tissue plasminogen activator.Other factors include the therapy-related factors and the concurrent infections that also play a role in the coagulopathy of AL.[5,6]

Acute promyelocytic leukemia (APL) is the most common subtype known to be associated with coagulopathy and bleeding, especially major bleeding, including CNS and pulmonary hemorrhage. The thrombotic events are generally low at presentation in AL, but the rate increases during the induction phase, especially with L-asparaginase used for ALL treatment, and this is due to impaired production of naturally occurring anticoagulantsthat may increase the thrombotic tendency in patients with ALL.[4,7]

As a result of the paucity of information on the coagulopathy of AL in our locality, this study was conducted to assess the coagulation markers in patients with different AL subtypes and to detect the incidence of bleeding and thrombotic events at presentation.

Methods

This prospective cross-sectional comparative study was carried out from September 2021 to May 2022 at Nanakali-Hemato-Oncology Center, Erbil, Iraqi Kurdistan. Fifty-nine newly diagnosed patients with de novo AL were enrolled in this studyat the time of presentation before starting any form of supportive or definite therapy, together with 35 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. Based on the immunophenotypic characteristics, confirmation and classification of AL were done using flow cytometry. Exclusion criteria were age less than 15 years, having a bleeding tendency or thrombophilia, organ failure, receiving therapy or anticoagulants, and being pregnant.

Full history and thorough examination were carried out for each patient, and data were recorded. Bleeding was 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 Stago coagulometer (STA Compact, France). Plasma D-Di-levels 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

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

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Results

A total of 59 patients with de novo AL were included in this study, of whom 31 patients (52.5%) were male. The control group consisted of 35 apparently healthy individuals of whom 23 (65.7%) were male. The mean (SD) age of the patients and controls were 41.4 (19.7) and 43.3 (12.7) years, respectively (Table 1).

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

Table 1 Characteristics of patients and control groups

Variables		Patients	Control	*P value*
Age (years)	Mean (SD)	41.4 (19.7)	43.3 (12.7)	0.516*
	Median (Range)	41.0 (15.0-81.0)	42.0 (18.0-72.0)	
BMI (kg/m^2)	Mean (SD)	26.6 (3.9)	25.4 (1.9)	0.10*
	Median (Range)	26.2 (16.6-41.8)	30.1 (20.9-27.7)	
Gender	Male No. (%)	31 (52.5)	19 (54.3)	
	Female No. (%)	28 (47.5)	16 (45.7)	0.870**

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

Table 2 Laboratory parameters of AML and ALL patients

Lab parameters	AML (n = 38)		ALL (n = 21)	
	Mean (SD)	Min-Max	Mean (SD)	Min-Max
Hematological parameters				
Hb (g/dl)	8.0 (1.7)	4.9-10.7	10.0 (2.5)	4.8-15.1
WBC (×10^9/L)	58.0 (81.5)	1.6-360	44.1 (82.2)	1.4-375.5
Platelet (×10^9/L)	56.7 (52.9)	8-268	70.2 (71.6)	6-308
Blast in PB (%)	50.3 (31.2)	0-98	45.8 (30.5)	0-90
Blast in BM (%)	86.0 (22.5)	23-96	80.7 (17.2)	23-98
ESR (mm/hr)	70.8 (35.1)	20-150	62.8 (39.5)	3-155
Coagulation markers				
PT (sec.)	18.3 (4.5)	10.1-33.0	15.0 (2.7)	10.4-21.9
APTT (sec.)	32.5 (8.1)	22.0-54.0	29.1 (5.0)	22.8-39.7
FBG (g/l)	2.5 (1.5)	0.55-7.2	2.6 (1.4)	0.5-6.0
D-Di (µg/ml)	11.2 (12.9)	0.2-59.8	9.8 (15.7)	0.5-73.0
PC (%)	77.9 (32.8)	33.0-162.0	116.9 (63.8)	24.0-276.0
PS (%)	77.3 (30.2)	19.1-146.1	84.5 (36.6)	20.1-173.0
AT (%)	87.8 (16.7)	55.0-114.4	101.6 (22.8)	59.9-141.0

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Table 3 shows the hemostatic parameters in AML and ALL patients. The predominant abnormality in both types was the raised D-Dilevels, followed by thrombocytopenia. Whereas prolonged APTT and hypofibrinogenemia were the least detected abnormalities in both AML and ALL. However, PC was significantly decreased in AML compared to ALL.

Table 3 Hemostatic parameters in AML and ALL

Parameters	AML No. (%)	ALL No. (%)	Total No. (%)	*P* value
Platelet count (×10^9/L)				
Normal (≥150)	3 (7.9)	2 (9.5)	5 (8.5)	
Decreased (<150)	35 (92.1)	19 (90.5)	54 (91.5)	1.000*
PT (sec)				
Normal (≤14)	6 (15.8)	8 (38.1)	14 (23.7)	
Prolonged (>14)	32 (84.2)	13 (61.9)	45 (76.3)	0.065*
APTT (sec)				
Normal (≤36)	29 (76.3)	19 (90.5)	48 (81.4)	
Prolonged (>36)	9 (23.7)	2 (9.5)	11 (18.6)	0.297*
FBG (g/l)				
Normal (≥1.5)	29 (76.3)	16 (76.2)	45(76.3)	
Decreased (<1.5)	9 (23.7)	5 (23.8)	14 (23.7)	1.000*
D-Di (µg/ml)				
Normal (<0.5)	3 (7.9)	1 (4.8)	4 (6.8)	
Increased (≥0.5)	35 (92.1)	20 (95.2)	55 (93.2)	1.000*
PC (%)				
Normal (≥70)	19 (50.0)	17 (81.0)	36 (61.0)	
Decreased (<70)	19 (50.0)	4 (19.0)	23 (39.0)	0.020**
PS (%)				
Normal (≥60)	25 (65.8)	16 (76.2)	41 (69.5)	
Decreased (<60)	13 (34.2)	5 (23.8)	18 (30.5)	0.406**
AT (%)				
Normal (≥80)	25 (65.8)	16 (76.2)	41 (69.5)	
Decreased (<80)	13 (34.2)	5 (23.8)	18 (30.5)	0.406**
Total	38 (100.0)	21 (100.0)	59 (100.0)	

*By Fisher's exact test. ** By Chi-square test.

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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; 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	18.3	4.5		A x B	0.004
	B) ALL	15.0	2.7		A x C	< 0.001
	C) Control	13.5	1.0	< 0.001	B x C	0.150
APTT (sec)	A) AML	32.5	8.1		A x B	0.580
	B) ALL	29.1	5.0		A x C	0.466
	C) Control	31.7	2.8	0.043	B x C	0.039
FBG (g/l)	A) AML	2.5	1.5		NA	NA
	B) ALL	2.6	1.4			
	C) Control	2.5	0.7	0.551		
D-Di (µg/ml)	A) AML	11.2	12.9		A x B	1.000
	B) ALL	9.8	15.7		A x C	< 0.001
	C) Control	0.2	0.2	< 0.001	B x C	< 0.001
PC (%)	A) AML	77.9	32.8		A x B	0.020
	B) ALL	116.9	63.8		A x C	<0.001
	C) Control	126.6	46.5	< 0.001	B x C	0.814
PS (%)	A) AML	77.3	30.2		NA	NA
	B) ALL	84.5	36.6			
	C) Control	81.3	15.9	0.496		
AT (%)	A) AML	87.8	16.7		A x B	0.008
	B) ALL	101.7	22.8		A x C	< 0.001
	C) Control	106.9	10.0	< 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.

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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 in APL patients compared to non-APL AML patients. While PS and AT were significantly lower in non-APL compared to APL. The comparisons between ALL subtypes did not show any significant differences.

Table 6 shows the associations of bleeding, thrombosis, and early death with AML and ALL. Bleeding events were significantly more in AML than in ALL, while thrombotic events did not show significant differences. Early death was higher in AML though it did not reach statistically significant levels.

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

Markers	AML (n = 38)		*P**	ALL (n = 21)		*P**
	APL Mean (SD)	Non-APL Mean (SD)		B-ALL Mean (SD)	T-ALL Mean (SD)	
PT (sec)	21.0 (6.3)	17.6 (3.9)	0.125	14.5 (2.6)	16.2 (3.0)	0.302
APTT (sec)	34.6 (11.8)	32.0 (7.1)	0.883	29.8 (5.1)	27.5 (4.6)	0.302
FBG (g/l)	1.7 (2.1)	2.7 (1.3)	0.005	2.5 (1.4)	2.8 (1.6)	0.850
D-Di (µg/ml)	9.5 (2.7)	11.6 (14.3)	0.335	11.6 (18.3)	5.2 (2.3)	0.622
PC (%)	74.7 (23.4)	78.6 (34.8)	0.912	114.7 (67.8)	122.4 (57.9)	0.519
PS (%)	102.5 (27.3)	71.6 (28.2)	0.015	93.1 (35.8)	63.1 (31.5)	0.132
AT (%)	102.1 (11.2)	84.5 (16.2)	0.006	99.1 (24.3)	108.1 (19.2)	0.682

* By Mann-Whitney U Test.

Table 6 Associations of bleeding and thrombosis with AML and ALL

Variables	AML No (%)	ALL No (%)	Total No (%)	*P* value
Bleeding				
Yes	25 (65.8)	5 (23.8)	30 (50.8)	
No	13 (34.2)	16 (76.2)	29 (49.2)	0.002**
Grading of bleeding				
Grade 0	13 (34.2)	16 (76.2)	29 (49.2)	
Grade 1	5 (13.2)	3 (14.3)	8 (13.6)	
Grade 2	13 (34.2)	2 (9.5)	15 (25.4)	
Grade 3	6 (15.8)	0 (0.0)	6 (10.1)	
Grade 4	1 (2.6)	0 (0.0)	1 (1.7)	0.010*
Thrombosis				
Yes	1 (2.6)	1 (4.8)	2 (3.4)	
No	37 (97.4)	20 (95.2)	57 (96.6)	1.000*
Early death				
Yes	10 (26.3)	1 (4.8)	11 (18.6)	
No	28 (73.7)	20 (95.2)	48 (81.4)	0.07*
Total	38 (100.0)	21 (100.0)	59 (100.0)	

*By Fisher's exact test. ** By Chi-square test.

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Discussion

Advances in AL treatment have rendered this disease potentially curable. However, the rate of early mortality is still high; this is partly owing to early hemorrhage and, to a lesser extent, thrombosis, which represents the distinct and complex underlying coagulopathy that manifests early in the course of AL.[4] This study has investigated several coagulation parameters in AL patients at the presentation prior to starting specific or supportive therapy.

In the current study, the median patient's age was 41 years which was quite similar to what was reported by Tawfiq et al.[9] Males were slightly more than females, and this was comparable to other studies in Sulaymaniyah and Palestine.[9-11] In this study cohort, almost two-thirds of the cases were of AML types, which was dissimilar to what has been reported by Gomez-Almaguer et al.[12]

In this study, variable coagulation marker abnormalities were detected at the time of presentation. The most detected abnormality is the raised D-Dilevels which indicate ongoing coagulation activation and fibrinolysis, followed by thrombocytopenia, which is mostly attributed to the failure of production due to BM invasion by the blasts. However, the pathophysiology of hemostatic derangements in AL is complex and multifactorial. The factors that contribute to the coagulopathy in AL include the increased procoagulant activity by the tissue factors, cancer procoagulants, and microparticles expressed by the leukemic cells besides the cytokine production that result in endothelial disruption, in addition to the proteolytic activity induced by the granules of the myeloblasts that promote the fibrinolytic activity.[4]The least detected abnormalities were the prolonged APTT and the hypofibrinogenemia because FVIII and FBG are positive acute phase reactants, and often require more time in AL patients before they begin to decline.[13] However, the findings of the coagulation parameters in this study showed some similarities and disparities to other studies reported in China and Bangladesh and this may be explained by the differences in the characteristics of the studied cohorts, including leukemic subtype, age, and gender.[14,15.]

The natural anticoagulants were reduced in around one-third of the cases, more pronounced in AML than ALL. The reduction of these anticoagulants could be attributed to the alteration in the hepatic synthesis towards the production of acute phase reactants. Besides, the cytokine production by the leukemic cells results in disruption of endothelium and down regulation of PC and PS.[7,16]

In this study, the D-Dilevels were significantly higher in both AML and ALL compared to controls. PT was significantly prolonged, and AT and PC were significantly lower in AML compared to ALL and control groups. Thus, AML cases had maximum derangement in hemostatic markers; this is quite similar to what has been reported by Franchini et al.[17] Within the AML group, significant hypofibrinogenemia was found in APL patients compared to non-APLAML. On the other hand, non-APL had significantly lower PS and AT levels; these findings were in agreement with a study by Lee et al.[18] These findings support the notion that coagulopathy in AL is somewhat type and subtype dependent.

Bleeding was significantly associated with AML as approximately two-thirds of the AML cases had bleeding manifestations at presentation. However, the incidence of bleeding in AML in this study was higher than that reported by other studies in Sulaymaniyah, Pakistan, and Serbia.[9,19,20] These variations may be because most of the studies were retrospective, and bleeding incidents might not have been appropriately recorded. The bleeding manifestations in ALL were lower than a quarter of the patients and most were of mild forms, same findings reported by Shalal et al.[21] However, the higher incidence of bleeding in AML compared to

ALL is primarily due to the biological nature of myeloblasts expressing more fibrinolytic activity by the protease release from the granules and the high expression of annexin II by the malignant myeloid cells compared to the lymphoblasts.[4] In this study, bleeding was predominantly of Grade 2 followed by Grade 1, while grades 3 and 4 were the least and observed among AML cases only.

The thrombosis rate in this study was low, keeping with the wide range of 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 whether the thrombosis is symptomatic or asymptomatic.[22]

Early death mainly occurred in patients with AML; the most encountered causes of death were major bleeding, disseminated intravascular coagulation, and infections. The death rate in this study was higher than what has been reported by a study done in China.[23]

Conclusion

Coagulation aberrations are common in patients with AL at presentation, more prominently in AML. Bleeding manifestations were more common in AML patients. The rate of thrombosis was relatively low. Early death was predominantly seen in AML cases. Larger multicenter studies are required to better assess coagulopathy and bleeding in newly diagnosed AL.

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Competing interests

The authors declare that they have no competing interests.

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