SJIF Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 9.
Issue: 2
Page N. 202-211
Year: 2025

Original Article www.wjahr.com

D DIMER – A NOVEL PREDICTOR OF DISSEMINATED INTRAVASCULAR COAGULATION IN ACUTE LEUKEMIAS. (AN OBSERVATINAL STUDY ON 81 ACUTE LEUKEMIA CASES)

[1*]Dr. Aastha Jain, [2]Dr. Vanita Kumar and [3]Dr. Komal Baghla

[1]Fellow, Oncopathology GCRI, Ahmedabad.
[2]HOD & Senior Professor, Department of Pathology, SPMC, Bikaner.
[3]Senior Resident, Department of Pathology, KEM Hospital, Mumbai.

Received date: 24 December 2024 **Revised date:** 13 January 2025 **Published date:** 02 February 2025

***Corresponding Author: Dr. Aastha Jain**

Fellow, Oncopathology GCRI, Ahmedabad.

ABSTRACT

Background: Leukemias are a group of life-threatening malignant disorders of the blood and bone marrow. Leukemia is the 10th most commonly diagnosed cancer worldwide with an incidence of 3, 51,000 new cases (2.8%). In India, lympho haematopoietic malignancies constitute 9.5% of all cancers in men and 5.5% in women, and the incidence of ALL and AML are 35% and 15% of all hematological malignancies respectively. Disseminated intravascular coagulation is responsible for most cases of clinically significant bleeding or thrombosis in acute leukaemia. Uniform criteria for diagnosing DIC were not present untill the ISTH proposed its criteria in 2001. Although this criterion was able to identify overt DIC but failed to diagnose cases of preclinical DIC. It has been revealed that haematological malignancies can change the levels of plasma molecules involved in coagulation and fibrinolysis, such as D-dimer. Acute myeloid leukemias (AML) are more commonly associated with DIC, but the association with acute lymphoblastic leukemia (ALL) has been recognized. D-dimer is a molecule as result of breaking down of excessive fibrin formation from the activation of coagulation system. There is evidence of increased activation of coagulation in patients with acute leukemia which is reflected by the increment of D-dimer levels. D dimer levels alone can be a significant marker to predict DIC in pateints of acute leukemia. **Materials and Methods:** We adopted a single criterion by using a single cutoff for D-dimer at a level of more than 0.5microgram/Ml (500 nanogram/mL). All patients with d dimer above 500 nanogram/ml were evaluated further on day 7 after recieving chemotherapy to find out further rise in d dimer levels. **Observation:** In this study, we found elevated D-dimer levels in acute leukemia patients at initial diagnosis. 46 out of 81 subjects (56.79%) had increased D- dimer levels, with a median of 1,000 (range 500-9,800) ng/mL. Further classification of subjects based on their diagnosis showed increased D dimer levels in 27 cases (75%) out of 36 with AML, and 19 cases (42.22%) out of 45 cases with ALL. The median D-dimer levels of AML patients was 950 (range 100-14,700) ng/mL and of ALL patients was 300 (range 100-3,800) ng/mL. D dimer levels post induction chemotherapy were again analysed on day 7, and 49 cases (60.49%) showed elevated D dimer levels with a median of 1,000 (range 500-14,700) ng/mL. Of these 49 cases, 31 cases (63.26%) belonged to AML subtype while the rest 18 cases (36.73%) belonged to ALL subtypes. The D dimer levels were found elevated above normal in both ALL and AML cases. **Discussion and Conclusion:** we find activation of coagulation system in children at the time of diagnosis of acute leukemia. More than half of patients with acute leukemia in our study show increased D-dimer levels at the time of initial diagnosis in both subtypes of leukemia establishing that ALL similar to AML predisposes patients to various hemostatic abnormalities which can lead to thromboembolic events and DIC is such patients which is further aggrevated by induction chemotherapy which casues further rise in D dimer levels due to tumor lysis, and such pateints often present with bleeding manifestations, some of which can prove life threartening. Hence serial evaluation of D dimer levels in acute leukemia patients can predict hemostatic complications.

KEYWORDS: AML, ALL, D-dimer.

INTRODUCTION AND BACKGROUND

Leukemias are a group of life-threatening malignant disorders of the blood and bone marrow. Leukemia is the 10th most diagnosed cancer worldwide with an incidence of 3, 51,000 new cases (2.8%) and 11th leading cause of cancer death worldwide with mortality

of 2,57,000 (3.4%) each year.[1] In childhood malignancy Leukemia is also the most common. It accounts for 30% of all cancers diagnosed in children under 15 years of age.[1] Developing countries bear more than half of global cancer burden, because 75% of the world population lives in these countries. In India, lympho-hematopoietic malignancies constitute 9.5% of all cancers in men and 5.5% in women, and the incidence of ALL and AML are 35% and 15% of all hematological malignancies respectively.[2]

In Leukemias the important manifestations are in form of anemia and/or thrombocytopenia with leukocytosis or in form of pancytopenia with presence of immature leukocytes in peripheral blood. When blasts cells are more than 20% in bone marrow and/or peripheral blood, the leukemia is designated as acute leukemia.[3]

Acute leukemia tends to present non-specifically, although the most common presenting features include fever, weight loss, bone pain, bruising, lethargy, and bleeding. Hepatosplenomegaly, lymphadenopathy, and musculoskeletal symptoms (especially in the spine and long bones) can also be clues to the diagnosis. Adults may also have more prominent anemia-related symptoms, such as shortness of breath, or symptoms related to thrombocytopenia, such as excessive bruising or heavy menstrual cycles.[4]

The diagnosis and classification of acute leukemia currently requires a combination of morphology, cytochemistry, immunophenotyping and cytogenetics (or molecular genetics) for complete diagnosis of many of the disease types. Multiple tests are needed to confirm a diagnosis, and subsequently, to stage the disease.

The occurrence of various coagulation abnormalities in acute leukemia is well established. Hemorrhage alone or because of disseminated intravascular coagulation (DIC) is the most common hemostatic disorder in patients with acute leukemia. The association of DIC with acute promyelocytic leukemia is particularly well documented. Up to 60% of leukemias may have some form of bleeding manifestations at presentation. Disseminated intravascular coagulation has been reported in 10% to 40% of patients at presentation in various series of patients with acute leukemias. The importance of recognizing this complication is for the institution of early therapy and prevention of hemorrhagic deaths in acute leukemia. Acute myeloid leukemias (AML) are more commonly associated with DIC, but the association with acute lymphoblastic leukemia (ALL) has been recognized.[5]

Hemostatic disturbances observed in patients with acute leukemias can be related to changes in vascular function, damage to the megakaryocytic system, liver dysfunction, increased fibrinolysis, and DIC.[5] The major hemostatic problem is usually hemorrhage secondary to thrombocytopenia, whereas thrombosis is a rare complication. Disseminated intravascular coagulation is responsible for most cases of clinically significant bleeding or thrombosis.

Although more commonly recognized in association with acute promyelocytic leukemia, all types of leukemias can trigger DIC. Malignant cells and chemotherapeutic agents used to treat acute leukemia are considered to have an important role in activating the coagulation system. Coagulation abnormalities occurring after institution of cytotoxic therapy for leukemia are a result of release of procoagulant substances from the leukemia cells.[6] The mechanism by which the malignant cells play a role in the pathogenesis of coagulopathy has not been completely clarified, although 2 hypotheses have been proposed. The first theory suggests that the granules of the malignant cells contain enzymes that can nonspecifically degrade proteins, including plasma coagulation factors. The second theory focuses on the presence of tissue factor−like material in the granules of leukemic cells that lead to activation of the coagulation cascade when they are released. In addition to tissue thromboplastin, cancer procoagulant, a cysteine protease with direct factor X−activating activity, represents the main pro coagulant of acute promyelocytic leukemia cells. Secretion of inflammatory cytokines by leukemic cells, introduction of cytotoxic chemotherapy, and concomitant infections can all produce DIC.[7]

D-dimer is a molecule as result of breaking down of excessive fibrin formation from the activation of coagulation system. There is evidence of increased activation of coagulation in patients with acute leukemia which is reflected by the increment of D-dimer levels. In addition to abnormal levels of coagulation factors such as fibrinogen, factor VIII, von Willebrand factor, factor XIII-A, and plasminogen-activator inhibitor-1, several investigators have documented abnormal expression of tissue factor on blast cells and circulating cancer procoagulant that is associated with the activation of coagulation system and increased thrombin generation in patients with acute leukemia. Several markers have been evaluated to document thrombin generation. Among these, the thrombin-antithrombin (TAT) complex and D-dimer have been used more often, with the former considered to be more specific.[8]

Therefore, the present study was conducted to determine the incidence of acute leukemias and various subtypes along with frequency of presenting clinical sign and symptoms and to establish a correlation between them with histopathological findings obtained after evaluation of peripheral blood smear and bone marrow aspirate smears. We also investigated the magnitude and clinical importance of haemostatic disturbances in acute leukemias by analysis of d- dimer levels at presentation and soon after receiving the induction chemo therapy.

METHODS

Study Design: This study was a hospital based

prospective study.

Study Place: The study was carried out at the Department of Pathology, Sardar Patel Medical College and Associated Group of Hospitals, Bikaner.

Study Period: The study was conducted for two years between February 2021 and February 2023.

Study Population: Patients of acute leukemia presented at PBM Hospital, Bikaner and whose investigations were received at Department of Pathology, in form of peripheral blood smear, bone marrow aspiration and d-dimer levels at the time of diagnosis and post induction chemotherapy.

Inclusion Criteria

All patients diagnosed with acute leukemias with adequate and representative Peripheral blood smears, Bone marrow biopsy specimens and D-dimer samples received at the Department of Pathology during the study duration.

Exclusion Criteria

1) Aspirates and d dimer samples of patients presenting with diagnosis other than acute leukemias.
2) Patients lacking any of the following investigation necessary to conduct the study – peripheral blood smear, bone marrow aspiration and d dimer levels along with details of clinical presentation and features.
3) Inadequate specimens with handling artefacts.
4) Patients unavailable or lost while follow up during study period.

The PBF smears were prepared from fresh venous blood sample of patient on a cleaned glass slide, properly fixed by air drying and then fixed with methanol and stained with leishman stain or field stain. Bone marrow smears are prepared on clean glass slides. The smears were then air dried and stained with leishman stain and one smear was fixed with methanol and stained with H&E stain.

D dimer blood samples are collected in 3.2% sodium citrate collection vial and then processed and d dimer analysis was done with Stago STA Compact Max.

Clinical details of the patients were obtained from the requisition form or medical records, including age, sex, habits, clinical examination, clinical diagnosis, IPT reports and other relevant reports and were noted.

RESULTS

The present study comprised of 81 cases of Acute Leukemia received at our department between February 2021 and February 2023. Clinicohematological details were obtained from each of the 81 cases the time of presentation and was evaluated prospectively on day 7 after receiving chemotherapy. Maximum number of cases belonged to age group of 1-20 years with percentage of 69.13%, while minimum number of diagnosed cases belonged to age group of above 80 years, with percentage of 2.77%. ALL is most common in the age group of 1-20 years, with a percentage of 91.11% while AML is most common again in the same age group of 1-20 years with a percentage of 41.66% followed by 21-40 years age group with 33.33%, in our study. [Image 1] The total Male cases of Acute lymphoblastic leukemia (ALL) were 30 in number, and Females were 15, accounting to 66.7% and 33.3% respectively. The total Male cases of Acute myeloid leukemia (AML) were 22 in number, and Females were 14, accounting to 61.6% and 38.9% respectively. [Image 2].

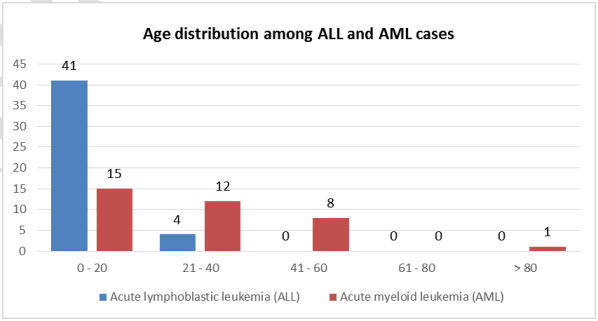

Image 1: Age distribution among ALL and AML.

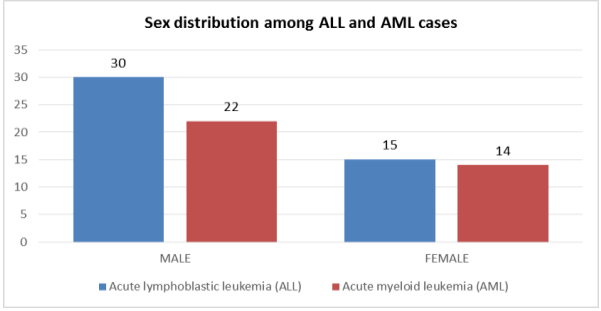

Image 2: Sex distribution among ALL and AML cases.

Table 1: Categorization of patients with Acute Leukemia as per French American British classification (n = 81).

TYPE OF ACUTE LEUKEMIA	SUBTYPE	NUMBER	PERCENTAGE
Acute Lymphoblastic Leukemia (ALL)	ALL-L1	31	75.60%
	ALL-L2	14	31.11%
	ALL-L3	0	0
	Total	45	55.55%
Acute Myeloid Leukemia (AML)	AML-M0	0	0
	AML-M1	1	2.8%
	AML-M2	15	41.7%
	AML-M3	14	38.9%
	AML-M4	6	16.7%
	AML-M5	0	0
	AML-M6	0	0
	AML-M7	0	0
	Total	36	44.45%

Out of total 81 cases, 45 (55.55%) were of Acute Lymphoblastic Leukemia (ALL), while 36 (44.45%) cases of Acute Myeloid Leukemia (AML). Maximum 31 (75.60%) cases of ALL belonged to L1 morphology, followed by L2 morphology with 14 (31.11%) cases. There were no cases of L3 morphology. The maximum number of 15 (41.7%) cases of AML belonged to M2 morphology, and minimum number of cases with 1 (2.8%) belonged to M1 morphology. No cases of M5, M6 and M7 morphology were reported. [Table 1].

Based on clinical findings on presentation, amongst 81 cases of Acute Leukemia, 79.01% (64) patients presented with pallor and fatigue followed by fever which was presenting feature in 69.13% (56) cases. 19 cases (23.45%) presented with bleeding at the time of initial diagnosis. [Image 3].

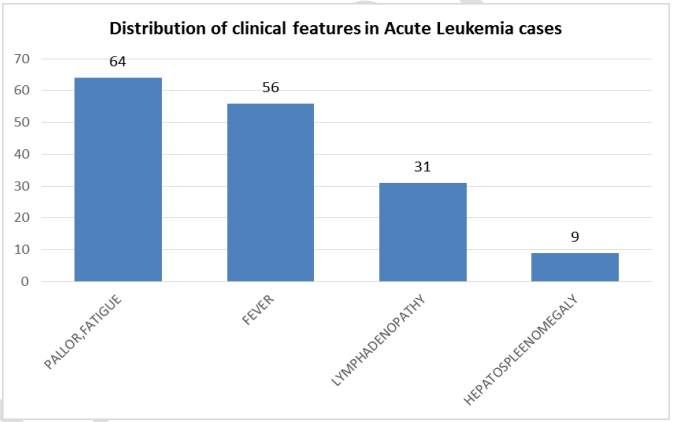

Image 3: Distribution of cases according to clinical features.

On complete hemogram study, anemia was present in 79 (97.53%) cases of acute leukemia with 7 cases (8.6%) having hemoglobin below 5gram/dl and 57 cases (70.4%) having hemoglobin between 5.1 to 10 gram/dl. Anemia was found to be more prevalent among ALL cases. [Table 2] On comparing the Total Leucocyte Count, it showed higher values of upto 50,000cells/cumm, in 40% cases of ALL and upto 10,0000cells/cumm in 6.7% of them. AML showed 50,000cells/cumm in 48.1% cases and higher counts of upto 10,0000cells/cumm in 4.9% cases. Both ALL and AML, had 13.3% and 9.9% cases respectively with a total count value upto 2,00000cells/cumm. [Table 2] On comparing the Platelet Count, at presentation, 33 patients (40.7%) had thrombocytopenia (platelet count < 1,00000 cells/cumm). Platelet counts were seen less than 50,000cells/cumm, in 13.3% of ALL, and in 16.0% of AML cases and 16.0% amongst all cases of acute leukemia. [Table 2].

Table 2: Hemoglobin levels among patients of various Subtypes of Acute Leukemia (*n* = 81)

	ALL		AML	
	NO.	%	NO.	%
Hemoglobin (gm/dl)				
1– 5	4	8.9%	3	8.3%
5.1– 10	34	75.6%	23	70.4%
10.1 – 15	7	15.6%	10	21.0%

15.1+	0	0.0%	0	0.0%
WBC Count				
<4000	5	11.1%	5	12.3%
4000 – 11000	11	24.4%	4	18.5%
11001 - 50000	18	40.0%	21	48.1%
50001-100000	3	6.7%	1	4.9%
100001-200000	2	4.4%	3	6.2%
> 200000	6	13.3%	2	9.9%
Platelet Count				
<=50000	6	13.3%	7	16.0%
50001 – 100000	11	24.4%	7	22.25%
100001 – 150000	8	17.8%	9	21.05%
150001+	20	44.4%	13	40.75%
TOTAL	45	100.0%	36	100.0%

On comparing percentage of blast cells on PBF and bone marrow aspiration, as shown in the below table, in ALL cases, L2 morphology showed maximum number of blasts with mean value of 77±11 %. In AML cases maximum blast were seen in M1 variant with 88% mean blast cells. Followed by M4 variant with 64±19 %. [Table 3].

Table 3: Percentage of Blast cells on peripheral blood smear and bone marrow aspiration (*n* = 81).

Type of acuteleukemia	Subtype	PBF		Bone Marrow Aspiration	
		Blast % -Mean	SD	Blast % -Mean	SD
Acute lymphoblastic leukemia(ALL)	ALL-L1	35	18	56	20
	ALL-L2	54	11	75	17
	ALL-L3	0	0	0	0
	Cumulative ALL cases	37	18	58	21
Acute myeloid leukemia (AML)	AML-M0	0	0	0	0
	AML-M1	60	0	88	0
	AML-M2	40	14	57	19
	AML-M3	35	14	55	18
	AML-M4	40	16	64	19
	AML-M5	0	0	0	0
	AML-M6	0	0	0	0
	AML-M7	0	0	0	0
	Cumulative AML cases	38	15	60	19

We found elevated D-dimer levels in acute leukemia patients at initial diagnosis. 46 out of 81 subjects (56.79%) had increased D-dimer levels, with a median of 1,000 (range 500-9,800) ng/mL. Further classification of subjects based on their diagnosis showed increased D dimer levels in 27 cases (75%) out of 36 with AML, and 19 cases (42.22%) out of 45 cases with ALL. The median D-dimer levels of AML patients was 950 (range 100-14,700) ng/mL and of ALL patients was 300 (range 100-3,800) ng/mL. [Table 4].

D dimer levels post induction chemotherapy were again analyzed on day 7. 49 cases (60.49%) showed elevated D dimer levels with a median of 1,000 (range 500-14,700) ng/mL. Of these 49 cases, 31 cases (63.26%) belonged to AML subtype while the rest 18 cases (36.73%) belonged to ALL subtypes. [Table 5].

Table 4: Mean D-dimer levels in acute leukemia patient at the time of presentation (*n* = 81).

TYPE OF ACUTE LEUKEMIA	SUBTYPE	Increased D- DIMER ng/ml No. of cases (%)	Median (Range)	p-value
Acute lymphoblastic leukemia (ALL)	ALL-L1	19 cases (42.22%)	300 (range 100-3,800) ng/mL	0.241
	ALL-L2			
	ALL-L3			
Acute myeloid leukemia (AML)	AML-M0	27 cases (75%)	950 (100-14,700) ng/mL	0.015
	AML-M1			
	AML-M2			
	AML-M3			
	AML-M4			

Table 5: Mean D-dimer levels in acute leukemia patient on day 7 of induction chemotherapy (*n* = 81).

TYPE OF ACUTE LEUKEMIA	SUBTYPE	Increased D- DIMER ng/ml No. of cases (%)	Median (Range)	p-value
Acute lymphoblastic leukemia (ALL)	ALL-L1	18 cases (36.73%)	214 (100-3,800) ng/mL	0.081
	ALL-L2			
	ALL-L3			
Acute myeloid leukemia (AML)	AML-M0	31 cases (63.26%)	3541 (100-14,700) ng/mL	0.027
	AML-M1			
	AML-M2			
	AML-M3			
	AML-M4			

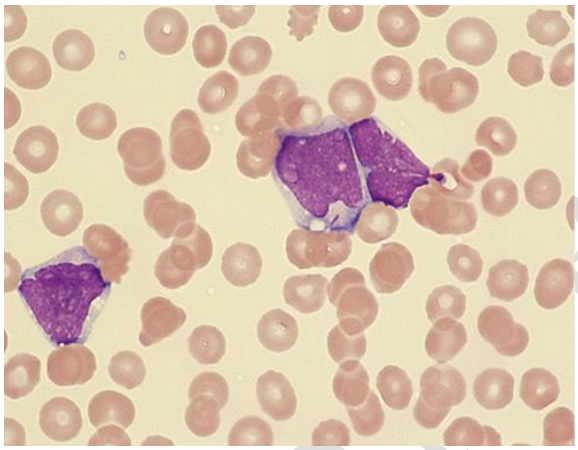

Image 1: PBF in AML showing myeloblast with auer rods in a nuclear hof. Field stains 100xs.

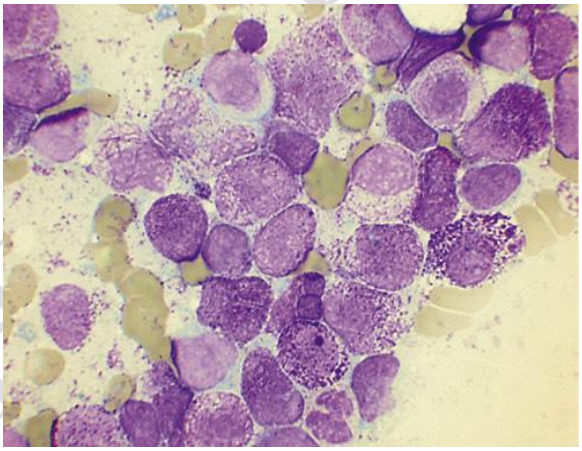

Image 2: Bone marrow aspiration smear in hypergranular APL showing hypergranular promyelocytes, with auer rods. Leishman 100X.

DISCUSSION

The incidence of leukemia has increased considerably, and this rise is noticeable because of improved statistics, better case findings with novel technologies which lead to better diagnosis and treatment methods. This incidence varies in different geographical regions according to varying lifestyles and economic conditions.

In India the incidence of various hematological cancers is different as compared to western countries. This can be attributable to less health awareness and poor availability of health care delivery system in India. Diagnosis of leukemia requires a multi parameter approach for its diagnosis, which includes cytomorphology study, with phenotypic and genotypic studies. In the present study 81 cases of acute leukemia, were evaluated, by studying their morphology, as well as clinical features and D dimer levels were assessed to predict underlying hemostatic abnormality in acute leukemia patients.

Of the 81 cases of Acute Leukemias included in our study, 45 were of Acute Lymphoblastic Leukemia -ALL (55.55%), and 36 were of Acute Myelogenous Leukemia-AML (45.45%). This indicates that ALL was more common than AML amongst all Acute Leukemia cases which correlates with study of Advani et al.[9]

Table 6: Comparison of AML subtypes with previous studies in the distribution.

FAB	Ghosh H et al. 2003[10]	Singh G et al. 2021[11]	M. U. Chowdhury et al. 2021[12]	Present Study 2023
M0	0	3.03	0	0
M1	35.5	7.5	16.7	2.8
M2	34	28.7	47.6	41.7
M3	5.4	50	0	38.9
M4	3.5	5.5	23.88	16.7
M5	20	3.03	4.8	0
M6	1.6	1.5	2.4	0
M7	0	0.75	0	0

After **subtyping of Acute Leukemias** based on morphology and using French American British (FAB) classification, the study showed that in ALL, 31 cases of L1(75.60%) and 14 cases of L2(31.11%) morphology were detected. No case of L3 morphology was detected amongst ALL cases. In AML, 1 case of M1 (2.8%), 15 cases of M2(41.7%), 14 cases of M3(38.9%), 6 cases of M4 (16.7%). No cases of M0, M5, M6 and M7 were detected. This showed that AML M2 was the commonest followed by M3 subtype, in the FAB classification, this finding is similar to other studies conducted as highlighted in table 6. [Table 6].

Gender distribution showed a male preponderance which correlates with the previous studies where male preponderance has been reported. The total Male cases of Acute lymphoblastic leukemia(ALL) were 30 in number, and Females were 15, accounting to 66.7% and 33.3% respectively. The total Male cases of Acute myeloid leukemia(AML) were 22 in number, and Females were 14, accounting to 61.6% and 38.9% respectively.

Age distribution for the diagnosed cases of Acute Leukemia shows maximum number of diagnosed cases of acute leukemia belonged to age group of 1-20 years with percentage of 69.13%, while minimum number of diagnosed cases belonged to age group of above 80 years, with percentage of 2.77%. ALL is most common in children and early adolescent in the age group of 1-20 years, with a percentage of 91.11% in our study while AML is most common again in the same age group of 1-20 years with a percentage of 41.66% followed by 21-40 years age group with 33.33%, in our study. These findings correlate with the previous studies which have shown that ALL is commonest in children and early adolescent age group as compared to AML which is much more common in adult age groups.

Table 7: Comparison with other studies.

Reference	Study
Neglia, jp, and Robison.10 1988[13]	In children, acute lymphoblastic leukemia (80%) is more common than acute myeloid leukemia.
Ribera JM, Oriol A.11 2009[14]	Acute lymphoblastic leukemia (ALL) is the most frequently diagnosed malignancy in children, representing nearly one third of all pediatric cancers.
Present study	Acute Lymphoblastic Leukemia is more common in age group of 0 to 20 years (92).

Table 8: showing the comparative study.

Reference	Study
Boros, L. and Bennett, J. M (1984)[15]	AML occurs twice as often as ALL, most cases occurring in adults.
Khalid Hassan Nadeem Ikram, Sajid Hussain Shah13 (1994)[16]	AML was observed more commonly in adults (79%) as compared to children (21%), whereas ALL was commoner in children (72%) as Compared to in 28% amongst adults.
Greer John P, Baer Maria. R, Kinney Marsha. C (2009)[17]	AML accounts for less than 15% of cases of leukemia in children below 10years, 25- 30% between 10-15 years, and in adults, it accounts for 80-90% of cases of acute leukemias.
Our study	Acute Myeloblastic Leukemias has an adult predominance (55.55%).

Laboratory hematological values

With correlation of laboratory values, **Haemoglobin** was seen to be less, and anemia was prevalent in as many as 79(%) cases of acute leukemia with 7 cases (8.6%) having hemoglobin below 5gram/dl and 57 cases (70.4%) having hemoglobin between 5.1 to 10 gram/dl, this clearly indicates severe anemia as a coexisting disorder, in cases of acute leukemia. The main

cause being inadequate production of red cells and shortened life span. Abnormalities of size and shape can also occur. ALL had as high as 38 (84.5%) cases with anemia and hemoglobin levels below 10 gram/dl, while AML showed 26(78.7%) of cases with anemia and hemoglobin levels below 10 gram/dl. Anemia was hence found to be more prevelant among ALL cases.

The **total leukocyte count showed** higher values of upto 50,000cells/cumm, in 40% cases of ALL and higher values of upto 10,0000cells/cumm in 6.7% of them. AML showed 50,000 cells/cumm in 48.1% cases and higher counts of upto 10,0000cells/cumm in 4.9% cases. Both ALL and AML, had 13.3% and 9.9% cases respectively with a total count value upto 2,00000cells/cumm. This signifies those elevated counts will have less mature cells, and more of the immature variety. Leucopenia is an uncommon feature.

Platelet counts in general are lower in Acute leukemias. This was interpreted in the study, and Platelet counts were seen less than 50,000cells/cumm, in 13.3% of ALL, and in 16.0%of AML cases and 16.0% amongst all cases of acute leukemia. This signifies that acute leukemias ends up with less production of platelets, with decreased survival, causing, thrombocytopenia.

The **distribution of clinical features** among patients diagnosed with Acute Leukemia was as follows - amongst 81 cases of Acute Leukemia ,79.01% (64) pateints presented with pallor and fatigue followed by fever which was presenting feature in 69.13% (56) cases. 19 cases (23.45%) were presented with bleeding at the time of initial diagnosis. These findings corelate with the study done by Ghosh S et al[10] where they found pallor and fatigue (82%) as commonest presenting clinical symptom and reported bleeding as a symptom in 21.9% patients.

Disseminated intravascular coagulation is responsible for most cases of clinically significant bleeding or thrombosis in acute leukemia. Although more commonly recognized in association with acute promyelocytic leukemia, all types of acute myeloid leukemias can trigger DIC. Uniform criteria for diagnosing DIC was not present until the ISTH proposed its criteria in 2001. Although this criterion was able to identify overt DIC but failed to diagnose cases of preclinical DIC. Also, because many molecular parameters are needed to diagnose DIC. In developing countries such as ours with limited resources available many laboratories are not equipped with the infrastructure to do these tests neither are they feasible economically. Also, studies conducted by Dixit A et al.[15] and Chowdhary M et al.[16] highlighted that platelet count and fibrinogen levels used in ISTH scoring system were assigned lesser scores and were better predictor of bleeding manifestation rather than DIC.

It has been revealed that hematological malignancies can change the levels of plasma molecules involved in coagulation and fibrinolysis, such as D-dimer. When initially diagnosed, serum **D-dimer** was found to be elevated in many patients, regardless of the type of acute leukemia. Also, D dimer levels were found to be significantly raised after patient received induction chemotherapy due to tumor lysis. However, the initially elevated D-dimer could be quickly lowered to a normal level after complete remission was achieved but may rise again in some cases of relapse or chemotherapy resistance.18 Because alterations in D-dimer were discovered during disease evolution, D-dimer values could likely to reflect or predict the prognosis of AML and ALL patients. As has been reported previously, D-dimer are elevated because of the release of enzymes or procoagulant materials from blasts or the fibrinolytic activity of the leukemic cells themselves. This is indicative of activation of coagulation systems in acute leukemia patients, as reported by authors from several developed countries.[17]

We adopted a single criterion by using a single cutoff for D-dimer at a level of more than 0.5microgram/mL (500 nanogram/mL) as was done by Dixit A et all in their study conducted at AIIMS, New Delhi. D dimer levels of all acute leukemia patients were assessed at the time of initial diagnosis. All patients with d dimer above 500 nanogram/ml were evaluated further on day 7 after receiving chemotherapy to find out further rise in d dimer levels.

In this study, we found elevated D-dimer levels in acute leukemia patients at initial diagnosis. 46 out of 81 subjects (56.79%) had increased D-dimer levels, with a median of 1,000 (range 500-9,800) ng/mL. Further classification of subjects based on their diagnosis showed increased D dimer levels in 27 cases (75%) out of 36 with AML, and 19 cases (42.22%) out of 45 cases with ALL. The median D-dimer levels of AML patients was 950 (range 100-14,700) ng/mL and of ALL patients was 300 (range 100-3,800) ng/mL. These findings were similar to study done by Harun Wijaya et all.[18] where out of 22 subjects, 13 subjects had increased D-dimer values.

Athale et al[19] reported a mean D-dimer level of 2,766 (SD 2,385.8) ng/mL in newly diagnosed case of ALL in children while Giordano et al.[20] reported a mean of 299 (SD 32) ng/ mL in children with ALL.1,2 Comparing the incidence of elevated D-dimer level in ALL, our finding was lower than Athale's but almost similar with the result of Giordano et al. Other studies reported that 80% of their subjects with ALL had elevated D-dimer levels.

D dimer levels post induction chemotherapy were again analyzed on day 7, and 49 cases (60.49%) showed elevated D dimer levels with a median of 1,000 (range 500-14,700) ng/mL. Of these 49 cases, 31 cases (63.26%) belonged to AML subtype while the rest 18

cases (36.73%) belonged to ALL subtypes. The D dimer levels were found elevated above normal in both ALL and AML cases although D dimer levels were statistically significant only in AML cases in our study with p value of 0.015 and 0.027 at the time of presentation and following induction chemotherapy.

This study was observational in nature. We did not evaluate a cause-and-effect relationship between diagnosis, the blast count subgroup and d dimer levels. Despite this limitation, our study provides a foundation for future studies in our country.

CONCLUSION

In our study we find activation of coagulation system in children at the time of diagnosis of acute leukemia. More than half of patients with acute leukemia in our study show increased D-dimer levels at the time of initial diagnosis in both subtypes of leukemia establishing that ALL similar to AML predisposes patients to various hemostatic abnormalities which can lead to thromboembolic events and DIC is such patients which is further aggravated by induction chemotherapy which causes further rise in D dimer levels due to tumor lysis , and such patients often present with bleeding manifestations, some of which can prove life threatening . Therefore, elevated D dimer levels at the time of initial diagnosis or during induction therapy are predictive of activation of coagulation system in patients of acute leukemia, both ALL and AML subtypes. Hence serial evaluation of D dimer levels in acute leukemia patients can predict hemostatic complications.

REFERENCES

1. Rathod K B, Kulkarni D G, Nakate L. “Spectrum of leukemia at tertiary care hospital.” IP J Diagn Pathol Oncol., 2020; 5(1): 40-43.
2. Magrath, I, and J Litvak. “Cancer in developing countries: opportunity and challenge.” Journal of the National Cancer Institute, 1993; 85(11): 862-74.
3. Jatav, Jagannath & Jain, Bharat & Niranjan, Amit. (2015). “Clinicopathological study of acute lymphoblastic leukemia- a mulitiparameter study” Journal of Evidence Based Medicine and Healthcare, 2: 8582-8585.
4. Lyengar V, Shimanovsky A. Leukemia. [Updated 2020 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2020; Available from: https://www.ncbi.nlm.nih.gov/books/NBK560490/.
5. Dixit, Ashish et al. “Disseminated intravascular coagulation in acute leukemia at presentation and during induction therapy.” Clinical and applied thrombosis/hemostasis: official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 2007 Jul; 13(3): 292-8.
6. Falanga A, Russo L, Tartari CJ. Pathogenesis and treatment of thrombohemorrhagic diathesis in acute promyelocytic leukemia. Mediterr J Hematol Infect Dis., 2011; 3(1): e2011068. doi: 10.4084/MJHID.2011.068. Epub; 2011 Dec 21; PMID: 22220265; PMCID: PMC3248345.
7. Barbui, T, and A Falanga. “Disseminated intravascular coagulation in acute leukemia.” Seminars in thrombosis and hemostasis 2001; 27(6): 593-604.
8. Wijaya, H., N. Chozie, and B. Hegar. “Activation of Coagulation System and D-Dimer Levels in Children with Acute Leukemia”. Paediatrica Indonesiana, Aug. 2014; 54(4): 227-31.
9. Kuashansky K, Lichtman MA, Prchal JT, Levi MM, Press OW, Burns LJ, Caligiuri MA, editors. Williams Hematology. 9th ed. New York: McGraw Hill; 2016; 35-7, 1275- 87, 1373-93, 1437-47, 1467-73, 1505-13, 1527-31.
10. Ghosh, S et al. “Haematologic and immunophenotypic profile of acute myeloid leukemia: an experience of Tata Memorial Hospital.” Indian journal of cancer, 2003 40(2): 71-6. teingh G et al. Int J Res Med Sci., 2016 Apr; 4(4): 1115-1118.
11. Singh, Gajender, Padam Parmar, Sant Prakash Kataria, Sunita Singh, & Rajeev Sen. “Spectrum of acute and chronic leukemia at a tertiary care hospital, Haryana, India.” International Journal of Research in Medical Sciences [Online], 2016; 4(4): 1115-1118.
12. Chaudhary SD, Chaudhary M, Dixit R. Hematological Disorders in Children. In: Chaudhary M, Chaudhary SD, editors. Essentials of Pediatric Oral Pathology. 1st ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2011.
13. Ahirwar R, Nigam RK, Malik R, Kothari S, Jain R. “Cytochemical Analysis in Leukemia”. J of Evolution of Med and Dent Sci., 2015 Aug; 4(64): 11146-56.
14. Deghady AAM, Mansour AR, Elfahham BAAAE. The value of cytochemical stains in the diagnosis of acute leukemia. Int J for Research and Health Sciences, 2016 May; 2(5).
15. Jawad RT, Hammody LJ, Sreih AK. Cytochemical stains benefit in the Diagnosis of Childhood Acute Lymphoblastic leukemia. World Journal of Pharmaceutical Research, 2015; 4(8).
16. Blackwell Science Limited. Clin. Lab. Haem., 1996 Jul; 18: 231-6.
17. Berlukar S, Mantravadi H, Manohar C, Kurien A. Correlation of morphologic and cytochemical diagnosis with flow cytometric analysis in acute leukemia. J Can Res Ther., 2013; 9: 71-9.
18. Wada H, Gabazza EC, Asakura H, et al. Comparison of diagnostic criteria for disseminated intravascular coagula- tion (DIC): diagnostic criteria of the International Society of Thrombosis and Hemostasis (ISTH) and of the Japanese Ministry of Health and Welfare for overt DIC. Am J Hematol., 2003; 74: 17-22.
19. Athale UH, Chan AK. Thrombosis in children with acute lymphoblastic leukemia: part I. Epidemiology of thrombosis in children with acute lymphoblastic

leukemia. Thromb Res., 2003; 111: 125–131.
20. Giordano P, Del Vecchio GC, Santoro N, et al. Thrombin generation in children with acute lymphoblastic leukemia: effect of leukemia immunophenotypic subgroups. Pediatr Hematol Oncol 2000; 17: 667–672.