

**DISSEMINATED INTRAVASCULAR COAGULOPATHY; A CONDITION TO  
MONITOR IN THE MANAGEMENT OF LEUKAEMIA PATIENTS**

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## ABSTRACT

**Background:** Disseminated intravascular coagulopathy is a consumption coagulopathy which mostly results from an underlying disease. It occurs as a result of the activation of the coagulation cascade leading to the formation of thrombi which results in haemorrhage due to the excessive consumption of platelet and coagulation factors. Malignancy is associated with hypercoagulable state and increased risk for thrombohemorrhagic complications and leukaemia is no exception. Bleeding manifestations are common in acute leukemias, especially in acute myeloblastic leukemia, and are prominent features of an initial stage of the disease. This study assessed disseminated intravascular coagulopathy (DIC) in leukaemia patients in Nigeria.

**Materials and Methods:** One hundred and sixteen (116) subjects consisting of 58 leukaemic subjects (AML, CLL, and CML) and 58 age and sex matched healthy control subjects were recruited into the study. The parameters estimated in this study were packed cell volume (PCV), platelet count, white blood cell count (WBC), prothrombin time (PT), international normalised ratio (INR), activated partial thromboplastin time (aPTT) and D-dimer assay.

**Result:** The mean  $\pm$  SD values of the parameters assessed in the leukaemia patients include  $3.74 \pm 3.13 \mu\text{g FEU/mL}$ ,  $67.59 \pm 55.71 \text{seconds}$ ,  $1.84 \pm 0.09$ ,  $77.34 \pm 31.81 \text{seconds}$ ,  $193.62 \pm 102.79 \text{cells/mm}^3$ ,  $74 \pm 124.42 \text{ cells/mm}^3$ ,  $30.07 \pm 5.38\%$  for D-dimer, PT, INR, aPTT, platelets, WBC and PCV respectively. The results display a significant statistical difference between the leukaemic and the control subjects ( $p < 0.05$ ).

**Conclusion:** The abnormality of these haemostatic parameters occurring in the leukaemic subjects (AML, CLL, and CML) is highly indicative of occurrence of disseminated intravascular coagulopathy in these patients. This study therefore shows that

disseminated intravascular coagulopathy can occur as a complication of various types of leukaemia studied and this require prompt and appropriate management.

Key Words: Disseminated intravascular coagulation, leukaemia, malignancy, and haemostasis.

## **INTRODUCTION**

Disseminated Intravascular Coagulation (DIC) is an abnormality characterized by the systemic intravascular activation of the coagulation system, simultaneously causing intravascular thrombi, distorting adequate blood supply to the organs, and bleeding as a result of exhaustion of the platelets and coagulation factors [1]. The clinical characteristics of DIC include spontaneous or induced bleeding complications and thrombotic complications, whereas multiple organ failures may be in part a complication of intravascular fibrin formation. Also, the generation of multiple proteolytically active enzymes of the clotting cascade may escalate inflammatory activity, which may increase the systemic inflammatory syndrome [2].

Various disorders including infections or inflammatory conditions and malignant disease can cause activation of coagulation. In several cases, this activation of coagulation may not cause clinical complications and may not even be detectable by routine laboratory analysis [3]. However, if activation of coagulation is sufficiently strong, a reduction in platelet count and extension of global clotting time may become evident [3]. The management of DIC is mainly directed at treating the underlying disease, but supportive care may be essential. This care may involve supplementing the platelets, reduced coagulation factors and endogenous coagulations inhibitors, inhibiting coagulation by different anticoagulant strategies and/or by exploiting the fibrinolytic system [4].

DIC could be initiated as a result of complication of some neoplastic diseases such as leukaemia and myeloproliferative disorders. Leukaemia is a group of malignancies that normally starts in the bone marrow and causes the production of raised numbers of abnormal white blood cells [5]. Leukaemia can be generally classified as acute or chronic and can additionally be classified as myeloid or lymphoid depending on the cell

line that is affected. The cause of leukaemia remains unidentified, however, a higher risk is associated with certain substances (e.g. benzene), large doses of ionizing radiation and infection with specific viruses (e.g., Epstein-Barr virus, human lymphotropic virus). Smoking cigarettes and exposure to electromagnetic fields also have been suggested as predisposing factors [6].

Of various forms of leukaemias, acute promyelocytic leukaemia (APL), a subtype of promyelocytic leukaemia (PML), has been associated with multiple haemostatic abnormalities [7]. Most, if not all, patients with APL have signs of DIC at the time of diagnosis. Patients with APL have an increased risk of death during initiation therapy when compared with patients with other forms of leukaemia, mostly due to bleeding. Unfortunately, outside of clinical trials the rate of early death in APL has not changed with the advent of new therapies [8].

Disseminated intravascular coagulopathy is a critical clinical condition and has been demonstrated in some individuals with acute leukaemia [9]. There is paucity of information on the presence of disseminated intravascular coagulopathy in different types of acute leukaemia and other forms of chronic leukaemia in this environment. It is, therefore, necessary to investigate DIC in individuals with different forms of leukaemia treatment for the possibility of management of DIC alongside leukaemia in such situations.

## **MATERIALS AND METHODS**

### **Subject Selection**

Fifty eight (58) patients comprising of 30 females and 28 males with acute myeloblastic leukaemia (AML), chronic lymphocytic leukaemia (CLL) and chronic myelocytic leukaemia (CML) who were newly diagnosed and at initial stage of chemotherapy were

recruited over a period of 8 months from the Federal Teaching Hospital, Ido-Ekiti, Nigeria and other specialist medical centres around while additional fifty eight (58) age-sex matched healthy individuals served as control subjects in this study. The patients distribution consist of 32 CLL, 24 CML and 2 AML patients with no patient with acute lymphocytic leukaemia (ALL) presented in the hospital during the patient recruitment period. Ethical approval and informed consent were obtained from the Federal Teaching Hospital Ido-Ekiti, Ekiti State and the participants respectively.

### **Blood samples collection and analysis**

Four millilitres (4 ml) of peripheral blood was collected from each participant with 2 mls dispensed into the 0.25ml of trisodium citrate anticoagulant (anticoagulant, blood ratio, 1:9) for the coagulation studies; 2 mls dispensed into EDTA contained vials for the complete blood count. The citrated blood for coagulation studies was separated by centrifugation at 1500 rpm for 15 minutes to obtain platelet rich plasma which was stored frozen at – 20°C until analysed.

The parameters estimated and their corresponding methods of analysis used in this study were packed cell volume, platelet and white blood cell counts using Abacus junior haematological autoanalyser; prothrombin time (PT), international normalised ratio (INR), activated partial thromboplastin time (aPTT) using Diagen reagents; D-dimer assay using Tina Quant Gen 2 D-dimer reagent on Roche Cobas C 111 analyser by immunoturbidometry technique.

### **Statistical Analysis**

The data generated was expressed as mean  $\pm$  SD. A p-value  $<$  0.05 was considered the significant levels of the statistical analysis using SPSS version 20.

## RESULTS

The results of this study show 30 female and 28 male leukaemic subjects out of which thirty-two (32) subject had CLL, twenty four subjects (24) had CML and two (2) subjects had AML . They aged between 35 and 65 years. The mean±SD values of various parameters estimated in all participants involved in this study are represented in Table 1. This reflects a significant difference in the clotting times between the patients when compared with the control subjects ( $p<0.05$ ). Platelet counts however reduced in the patients than the control subjects though not statistically significant.

Additionally, the PT and aPTT distribution among the D-dimer level in the leukaemic subjects is represented in Table 2. It was observed that fifty (86%) of the patients had increased D-dimer and prolonged PT while forty-eight (82%) had increase D-dimer and prolonged PTTK with five (9%) having a prolonged PT, aPTT, INR and increased D-dimer level. These five (5) subjects were also observed to present with thrombocytopenia.

The mean ±SD values of PT, aPTT, D-dimer , platelet count, PCV and WBC in the female and male patients are  $81.33\pm67.39$ ,  $83.33\pm34.09$ ,  $3.78\pm3.53$ ,  $167.93\pm90.27$ ,  $27.93\pm5.61$  ,  $77.75\pm139.58$  and  $52.86\pm36.64$ ,  $70.93\pm29.01$ ,  $3.69\pm2.78$ ,  $221.14\pm111.38$ ,  $32.07\pm4.45$  and  $77.75\pm139.58$  respectively. This result displays no significant difference in the variables except in PCV ( $p=0.03$ ).

Table 1: Mean±SD of estimated Parameters in the Leukaemia patients and control subjects.

Parameters	Patients n=58 Mean±SD	Control n=58 Mean±SD	t-test	p-value
D-dimer(µg FEU/mL)	3.74±3.13	0.31±0.18	5.888	0.001
PT(seconds)	67.59±55.71	13.10±1.06	5.266	0.001
<b>INR</b>	<b>1.84±0.09</b>	<b>1.11±0.02</b>	<b>7.705</b>	<b>0.001</b>
aPTT(seconds)	77.34±31.81	31.19±2.16	7.796	0.001
Platelet count (cells/mm <sup>3</sup> )	193.62±102.79	233.69±59.34	1.818	0.074
WBC(cells/mm <sup>3</sup> )	74±124.42	5.08±1.34	3.506	0.001
PCV (%)	30.07±5.38	37.80±4.63	5.870	0.001

ABBREVIATIONS= PCV (Packed Cell Volume), WBC (White Blood Cell Count), PT (Prothrombin Time), PTTK (Partial Thromboplastin Time with Kaolin), INR (International Normalised Ratio).



Table 2: Distribution of D-dimer levels among the PT and aPTT levels in the leukaemia subjects.

		D-dimer (n=58)		
		NORMAL	HIGH	p- value
PT	NORMAL	0	2	0.731
	HIGH	6	50	
aPTT	NORMAL	0	4	0.619
	HIGH	6	48	

PT (Prothrombin Time), PTTK (Partial Thromboplastin Time with Kaolin)

## DISCUSSION

DIC is a dynamic process and the analysis performed shows only the conditions at a given moment in time [10]. In clinical conditions associated with DIC, repeating the tests performed initially helps in establishing the diagnosis. Analysis performed in assessing the haemostatic state give information about the clinical course and the diagnosis is established based on clinical suspicion and supportive laboratory analysis [10]. The analyses performed include laboratory parameters indicative of procoagulant and fibrinolytic substance activation, inhibitor consumption and organ damage or failure [11].

Malignancy is associated with a hypercoagulable state and a high risk for thrombohemorrhagic complications. Its clinical complications may range from localized thrombosis to bleeding of varying degrees of severity because of DIC with life-threatening bleeding being frequent in acute leukemia, particularly in APL [12].

Laboratory assessments show profound hemostatic imbalance in this condition, with activation of coagulation, fibrinolysis, and nonspecific proteolysis systems [12].

This study evaluated some coagulation parameters to assess DIC in leukaemia patients which are; PT, INR, aPTT, platelet count, PCV and D-dimer assays. It was observed that the patients had a lower PCV ( $p < 0.05$ ) and platelet ( $p > 0.05$ ) values when compared with values obtained in the control subjects (Table 1) and this possibly reflects anaemia of chronic disease in the leukemia patients or that of cytotoxic therapy being administered. This established fact was validated by a previous study carried out by Akanni *et al.* (2010) [13] where a significantly low PCV was observed in values of leukaemic patients when compared with controls.

The reduced mean $\pm$ SD values of platelet count (though insignificant when compared with control) observed is also suggestive of excessive platelet consumption which is indicative of likely onset of DIC, resulting in the platelets being excessively consumed, hence bleeding. In 2014, Sadik *et al.* (14)., reported some similar corroborating multicenter meta-analysis studies where the researchers specified that the most frequently encountered abnormal laboratory findings in DIC were thrombocytopenia, increased fibrin degradation products, prolonged PT, aPTT and low fibrinogen levels [15, 16,17,18,].

The PT, aPTT and INR of the leukaemia patients in this study were found to be significantly prolonged ( $p < 0.05$ ) than those of the control subjects which were within normal range (Table 1). This is presumably due to the exhaustion of some coagulation factors involved in the extrinsic pathway along with thrombocytopenia in some of the leukaemia subjects which is due to DIC. This finding is similar to the report of another study carried out among Sudanese by Amr *et al.* (2014) [19], where they discovered the

leukaemia subjects to have prolonged coagulation parameters than controls ( $p < 0.05$ ).

Sadik *et al.* (2014) also concluded in their study that prolonged PT, aPTT and INR is a common finding in DIC [14].

The increased D-dimer level along with the prolonged PT/aPTT observed in the leukaemia participants in this study indicates increased fibrin deposition by coagulation process resulting in an increased fibrinolytic activity. Since D-Dimer is a fibrin degradation product hence an increased D-Dimer level is a diagnostic factor of DIC.

The sex distribution for the WBC, platelet and the haemostatic parameters carried out in this study displays an insignificant statistical difference between the genders which infers that gender has no effects on these parameters measured. Expectedly, there was a statistically significant difference ( $p < 0.05$ ) in the PCV, suggesting that gender plays a major role in the PCV values of the subjects.

Furthermore, some patients were observed to have both increased D-dimer and prolonged PT level while some had both increased D-dimer and prolonged aPTT level (Table 2) indicating the likely development of DIC among these population. Also, about 9% of the studied population have prolonged PT, PTTK, INR, increased D-dimer level and thrombocytopenia establishing the onset of DIC symptoms which is evidenced by some bleeding episodes experienced by the patients. This observation is corroborated by a study that ascertained the prolonged PT/PTTK and D-dimer as diagnostic tools for DIC [10].

In conclusion, majority of the haemostatic parameters analysed in the leukemic patients were observed to be abnormal, with the PT, aPTT, INR being very prolonged and D-dimer level elevated while the platelet count decreased below the normal level (though insignificant) in some of the subjects. These trends of results are characteristic of DIC

and indicative of the condition as a result of an impaired haemostatic activity in most of the leukemic subjects recruited in the study. This study has therefore revealed strong evidence of possibility of DIC in individuals suffering from various types of leukaemia condition (ALL, CLL and CML) regardless of their gender and treatment status.

It is therefore recommended that in the management and treatment of leukemia patients, DIC should be carefully screened and monitored in this region as it is being done in the developed world health management system. This will ensure possible detection of its occurrence at the onset and will promote adequate management of the disorder.

#### **ACKNOWLEDGEMENT**

We wish to appreciate the efforts of Miss Ogunbusuyi B. and Mrs Adeyemi O. of Haematology Laboratory, Department of Medical Laboratory Science, Afe Babalola University, Ado Ekiti, Nigeria. We are also grateful to Dr Muheeb M.A, Head of Medical Laboratory Services, Messrs' Agbaje and Moronkeji of Chemical Pathology LAUTECH teaching hospital, Osogbo, Nigeria for their contributions to the success of this study.

#### **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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