
Diagnosis of Chronic Disseminated Intravascular Coagulation in 72 Cancer Patients According to the International Society on Thrombosis and Hemostasis Score System

Ahmed, M. Amin, BSc, MSc *

Hisham, A. Getta, MBChB, FICMS **

Abbas H. Abdulsalam, MBChB, MSc ***

ABSTRACT

Background: Chronic disseminated intravascular coagulation (DIC) is a well- recognized life- threatening haemostatic complication that occurs frequently in patients suffering from Cancer.

Aim of the study: Evaluation of the diagnosis of chronic DIC, according to the International Society on Thrombosis and Hemostasis (ISTH) score system.

Methods: From July, 2006 to April, 2007, 72 pre-operative and pre-treatment patients with hematological and solid tumor malignancies, presenting to the Hewa Hospital for Oncology in Sulaimani, and 16 healthy volunteers served as controls were included in this study for the diagnosis of chronic DIC according to the ISTH score system.

Results: Among screened patients, a total of 30 (42%) were diagnosed with chronic DIC, which were solid tumors and hematological malignancies.

Conclusions: There is a high frequency of chronic DIC among pretreatment and preoperative cancer patients. This study is the first that used ISTH score system for the diagnosis of chronic DIC in cancer patients.

Keywords: Chronic DIC, ISTH diagnostic score system, cancer.

Introduction:

Disseminated intravascular coagulation, frequently designated by its acronym DIC¹, is the currently accepted nomenclature for a syndrome², which is not a disease itself but is always secondary to a wide variety of clinical conditions, the most important of which are sepsis, trauma, malignancy, organ destruction, obstetrical calamities, vascular abnormalities, hepatic failure and severe toxic or immunological reactions^{3, 4}. These disease entities may trigger DIC in their own distinctive manner, but the result remains the same; imbalance between coagulation, anticoagulation, and fibrinolysis⁵.

DIC may be chronic, in which the primary manifestation is thrombosis rather than bleeding. Patients with solid tumors, especially mucin-producing tumors, commonly suffer from chronic DIC^{6, 7} or DIC may be acute, often associated with life threatening hemorrhagic disorder, as in patients with acute promyelocytic leukemia (APL).

Significant controversies exist in regard to the diagnosis of DIC. However, DIC can be diagnosed on the basis of clinical and laboratory findings⁸.

There is no single laboratory test available today that is sensitive or specific enough to allow a definite diagnosis of DIC⁹. The laboratory tests used for the diagnosis of patients with DIC include; platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen level, fibrin/fibrinogen degradation products (FDP), D-Dimer and examination of a blood film to check for the presence of fragmented red cells or schistocytes¹⁰.

As acute DIC may play a significant role in the development of multiple organ failure¹¹, and in cancer patients, chronic DIC may progress to acute DIC due to radiation or chemotherapy, surgery, and advanced disease stage¹², therefore early diagnosis of this disorder plays a pivotal role in reducing its high mortality¹³.

Aim of the study:

Evaluation of the diagnosis of chronic DIC, according to the International Society on Thrombosis and Hemostasis (ISTH) score system.

Materials and methods:

The study included 72 pre-operative and pre-treatment patients with hematological (5 Hodgkin lymphoma, 3 non-Hodgkin lymphoma, and 2 chronic myelocytic leukemia) and solid tumor (23 gastrointestinal, 13 genitourinary, 12 breast, 6 lung, 2 bronchus, and 6 mesillanous) malignancies, who were suspected of having chronic DIC, presenting to the Hewa Hospital for Oncology in Sulaimani, between July, 2006 and April, 2007. There were 31 males (43%) and 41 females (57%), with a median age of 55 years, ranging from 20 to 81 years.

Meanwhile, 16 healthy volunteers served as controls (9 males and 7 females, median age 36 years, ranging from 27 to 70 years). Verbal approval was obtained from all patients. In case of impaired consciousness, consent was obtained from a family member or the closest relative or partner of the patient.

The pathologic diagnosis was made in accordance with World Health Organization classification of malignancies.

Blood Collection:

Blood samples were collected by venous puncture. For coagulation parameters, the samples were anticoagulated with 3.2% trisodium citrate (14) (4.5ml blood into 0.5ml trisodium citrate as a 9:1% vol/vol blood/anticoagulant).

Platelet-poor plasma was prepared from citrated samples immediately after venipuncture by centrifugation for 10 minutes at 2000g at room temperature¹⁵. Plasma was transferred to plastic tubes, frozen and stored at -40 C° until evaluated.

Refreezing and thawing were avoided. For complete blood count, blood was collected into ethylenediaminetetraacetic acid (EDTA)-anticoagulated tubes (AFMA-DISPO, Jordan). Blood was collected into citrated tube, and then into the EDTA tube¹⁶.

Blood coagulation assays:

The following assays: PT, and fibrinogen performed manually with clot-based assay kits using PT kit (Fischer Diagnostics®, USA), and fibrinogen kit (Mahsa-Yaran, Iran), respectively. D-Dimer levels were measured by quantitative immuno-assay using ELISA kit (Zymutest D-Dimer kit, Hyphen BioMed, France). Washing instrument (Beckman

Coulter AD 340, Austria) & reading instrument (Beckman Coulter MW 96, Austria) have been used.

Complete blood counts were measured by using automated hematology analyzer (Coulter: K-1000, Japan).

Diagnosis of DIC was made based on criteria proposed by the International Society on Thrombosis and Hemostasis (Table 1.1)¹⁷. Cumulated score of 5 or greater is recommended by the ISTH as indicative of overt DIC. While the score of less than 5 is considered suggestive (not affirmative) for non-overt DIC, preliminary evidence indicates that the early DIC or non-overt DIC can be captured¹⁸. The score points had been assigned as in Table 1

Table 1: Diagnostic criteria for Disseminated Intravascular Coagulation, 5-step Diagnostic Algorithm to calculate a DIC score¹⁹.

1. Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC? If yes: proceed; if no: do not use this algorithm.
2. Order global coagulation tests (platelet count, prothrombin time (PT), fibrinogen, soluble fibrin monomers or fibrin degradation products)
3. Score global coagulation test results:
 - Platelet count ($>100 = 0$; <100 but $\geq 50 = 1$; $<50 = 2$)
 - Elevated fibrin-related marker e.g. soluble fibrin monomers/fibrin degradation products (no increase: 0; moderate increase: 2; marked increase: 3)
 - Prolonged prothrombin time (<3 sec. = 0; >3 sec. but <6 sec. = 1; >6 sec. = 2)
 - Fibrinogen level (>1.0 g/l = 0; <1.0 g/l = 1)
4. Calculate score.
5. If ≥ 5 : compatible with overt DIC; repeat scoring daily.
If <5 : suggestive (not affirmative) for non-overt DIC; repeat next 1–2 days.

Statistical Analysis:

Analysis of data was performed by using SPSS (Version 11.5). Results are expressed as mean $\pm$ standard deviation (mean $\pm$ SD). Statistical differences were determined by Duncan's test for multiple comparisons between the three groups of malignant patients, chronic DIC, non-DIC positive D-Dimer, and non-DIC negative D-Dimer, after analysis of variance (ANOVA).

Independent unpaired student t -test was used to analyze the difference between control cases and malignant patients on the studied parameters. P value less than 0.05 regarded as statistical significant.

Results:

As shown in table 2, the means of PT (15 ± 3 seconds), fibrinogen (3 ± 1 g/L), and D-Dimer (3708 ± 3236 ng/mL) and platelets ($286 \pm 144 \times 10^9/L$) among patients with malignant disorders were significantly higher ($P < 0.05$) in comparison to the control group 13 ± 1 seconds for PT, 2.3 ± 0.6 g/L for fibrinogen, 325 ± 365 ng/mL for D-Dimer, and $212 \pm 46 \times 10^9/L$ for platelet.

Table 2: Comparison between blood coagulation test results in controls and malignant patients (Mean $\pm$ SD).

Parameters	Controls $\pm$ SD (n: 16)	Cancer Cases $\pm$ SD (n:72)	P- Values
PT (sec)	13 ± 1	15 ± 3	0.002
F (g/L)	2.3 ± 0.6	3 ± 1	0.012
D-Dimer (ng/mL)	325 ± 365	3708 ± 3236	0.0001
Platelet ($\times 10^9/L$)	212 ± 46	286 ± 144	0.047

Thirty out of 72 patients (42%) were diagnosed as chronic DIC (figure 1).

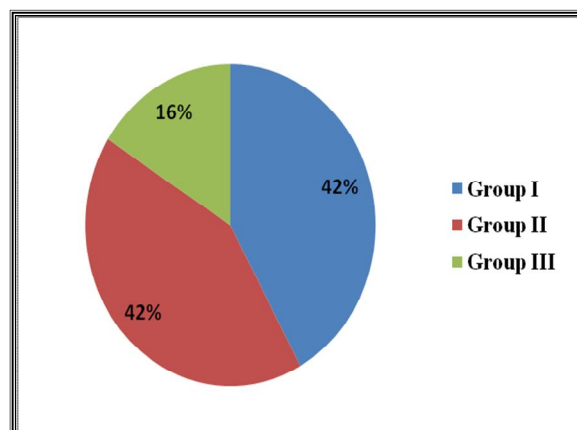


Figure 1: Percentage of chronic DIC among cancer patients.

Among these 30 patients, those who met the overt DIC criteria (score ≥ 5), they were regarded as chronic DIC because of the absence of any sign of bleeding.

The cases of DIC were patients with solid tumors (17 gastrointestinal, 3 breast, 2 lung, 3 genitourinary) and hematological (2 Hodgkin lymphoma, 2 non-

Hodgkin lymphoma and 1 chronic myelocytic leukemia).

As a result, and according to the value of D-Dimer, cancer patients were grouped into chronic DIC (Group I, n: 30), non-DIC positive D-Dimer (Group II, n: 30), and non-DIC negative D-Dimer (Group III, n: 12) groups.

Group I were associated with significantly ($P < 0.05$) elevated levels of D-Dimer (6313 ± 3210 ng/mL) in comparison with Group II (2438 ± 1425 ng/mL) and Group III (371 ± 156 ng/mL).

Furthermore, the comparison between the later two groups showed a significant difference. Group I patients were also associated with significantly ($P < 0.05$) prolonged PT (16 ± 3 sec) in comparison with PT of Group II patients, 14 ± 1 sec and of Group III, 14 ± 2 sec. The means of PT of Group II and Group III patients were non-significantly different. Fibrinogen concentrations in Group I patients (3.2 ± 1 g/L) were significantly increased when compared with Group III (2.4 ± 0.6 g/L) whereas it was not significant comparing with Group II (2.9 ± 1 g/L).

It was found that all three groups of the patients did not show significant differences ($P < 0.05$) in platelet count when they were compared to each other (Table 3).

Table 3: The comparison of means ($M \pm SD$) of coagulation parameters among malignant patients with chronic DIC, non-DIC D-Dimer positive, and non-DIC D-Dimer negative.

Parameters	Chronic DIC (Group I) (n: 30)	Non-DIC Positive D-Dimer (Group II) (n : 30)	Non-DIC Negative D-Dimer (Group III) (n: 12)
D-Dimer (ng/mL)	6313 ± 3210^a	2438 ± 1425^b	371 ± 156^c
PT (sec)	16 ± 3^a	14 ± 1^b	14 ± 2^b
Fibrinogen (g/L)	3.2 ± 100^a	2.9 ± 1^{ab}	2.4 ± 0.6^b
Platelets ($\times 10^9/L$)	318 ± 193^a	272 ± 97.24^a	240 ± 76^a

^{a, b & c} Common superscripts in the same row indicate non-significant difference ($p < 0.05$) between them. While different superscripts refer to the existence of a significant difference.

DISCUSSION

Under physiologic conditions, normal function of the human hemostatic system is well regulated and maintained by the actions of pro- and anticoagulant forces²⁰. In cancer patients, this delicate balance may be altered and provides a growth advantage to tumors²¹ suggesting that disorders of coagulation are very common in this disease, although clinical symptoms occur less frequently, which account for a significant percentage of the morbidity and mortality of the disease²². Therefore, it would be theoretically

and clinically desirable to have reliable tools for monitoring coagulation activation in cancer patients.

In the present study, coagulation abnormalities occurred in 63 (88%) out of 72 cancer patients.

Similar results have been reported by Gouin-Thibault and Samama²³ and Sun *et al.*,²⁴ they showed that approximately 90% and 92% of cancer patients have abnormal coagulation parameters, respectively.

The hemostatic markers PT, Fibrinogen, D-Dimer, and platelets were significantly higher in cancer patients compared to the controls (Table 1).

These results revealed that hemostatic disorders are frequent in cancer patients.

Activation of coagulation system by MET oncogene in a mouse model has been demonstrated²⁵. In this model it has been reported that activated MET oncogene not only caused a neoplastic transformation and development of cancer but also induced a hypercoagulable state, recording additional evidences that the hemostatic changes is frequent in cancer patients.

Although DIC was first observed in the 19th century²⁶, only recently have an international diagnostic standard and a useful scoring system become available. In 2001, clinical and laboratory criteria and a scoring system for DIC were published by ISTH¹⁷.

The non-overt DIC criteria include molecular markers such as antithrombin and protein C. Our laboratory could not measure routinely these molecular markers and ISTH has not strictly established them. Furthermore Hayakawa *et al.*, reported that the non-overt DIC criteria are not sufficient for the early diagnosis of DIC²⁷. Consequently, the non-overt DIC criteria were not used in this study, instead overt DIC criteria were used and a score of less than 5 are regarded as a suggestive of chronic DIC.

In the present study, 30 (42%) patients, in a population of 72 patients with malignant solid and hematological tumours, considered to have chronic DIC (Figure 1). This indicates that chronic DIC is not a rare disorder in cancer patients. Pavlovskii reported 56% in a population of 70 patients with stomach and intestinal cancer²⁸ and Kopanski *et al.*, reported 83% in a group of 80 stomachs or of the large bowel advanced age cancer patients²⁹ (aged 65 to 87 years). Three reasons for this difference were suspected. The first one is the type of tumours, for example, gastrointestinal cancers are mucin-produced carcinoma and these types of cancer are known to be common cause of chronic DIC³⁰. The second, as mentioned in the Kaponski and coworkers study, patients were advanced age (65-87) and treated with chemotherapy and both of these two factors are co-morbid variables for increasing incidence of chronic DIC²². The third reason is that factors such as patient selection, the sensitivity and timing of coagulation tests utilized, could markedly influence results and perhaps account for some of the reported discrepancies.

Comparison between the three groups (I, II, and III), demonstrated that the malignant patients with chronic DIC were associated with significantly elevated levels of D-Dimer (6313 ± 3210 ng/mL) as compared with non-DIC positive D-Dimer (2438 ± 1425 ng/mL) and non-DIC negative D-Dimer (371 ± 156 ng/mL) ($P < 0.05$) indicating that D-Dimer alone is sensitive but not specific in the diagnosis of chronic DIC because all the chronic DIC cases were reported to have elevated D-Dimer levels, at the

same time 30 cases out of 72 cases were also reported to be with elevated D-Dimer levels. Chronic DIC patients were also associated with significantly ($P < 0.05$) prolonged PT in comparison with non-DIC positive D-Dimer patients, meaning that PT is the second sensitive parameter for the diagnosis of chronic DIC.

While platelets and fibrinogen are of limited value because they failed to reach the significant difference among the three groups.

This might explain that why the DIC subcommittee of ISTH in their annual report on 2005 have suggested that fibrinogen might be removed from the score³¹.

Conclusion:

This study is the first that has been used ISTH score system for the diagnosis of chronic DIC in cancer patients. The impact of this study on the use of mild anticoagulation in this setting of cancer and DIC should be seriously considered. Further studies are required to solve this dilemma.

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* Department of Biology, College of Science; University of Sulaimaniya (hmdmuhamad@yahoo.com).

** Department of Pathology, College of Medicine; University of Sulaimaniya.

*** Department of Teaching Laboratories; Al-Yarmouk Teaching Hospital