THE CRITICAL ANALYSIS ON DIAGNOSIS OF DISSEMINATED INTRAVASCULAR COAGULATION WITH SCREENING TESTS–A SCORING SYSTEM AND RELATED LITERATURE REVIEW

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Background: The aim of this study is to assess confidence in the diagnosis of Disseminated Intravascular Coagulation (DIC); to evaluate the clinical significance of the haemostatic tests; to disclose any respective associations of such tests with patients' prognosis; and to review the related literature. It is a retrospective case series study in Changhua Christian Hospital, Taiwan. **Methods:** Ninety-four patients' data were analyzed. A scoring system was constructed retrospectively. **Results:** Hypotheses were postulated and proved. Each patient had a minimal score of 5, whereas those patients who had reached (increased) their scores were to the full or even over the maximal level (6 or 9) respectively. There was almost no correlation between age and Prothrombin Time (PT). The correlation between age and platelet count, and that between age and fibrinogen were positively minor respectively, whereas that of Activated Partial Thromboplastin Time (APTT) was +0.208. The correlations between APTT and PT, platelet count, fibrinogen respectively were significant. About 45.67% of patients had plasma fibrinogen >200 mg/dL, while 22.23% had <100 mg/dL. A paradox was observed. The finding of such a limited package of the screening tests was discussed. Related literature with regard to the clinical significance and pitfalls, as well as limitations and strengths of these haemostatic tests were reviewed and evaluated. **Conclusion:** There are 14 points of impression with clinical significance outlined.

Keywords: DIC, Surgical Intensive Care Unit, Laboratory diagnosis, Haemostatic test, Screening test.

INTRODUCTION

Disseminated Intravascular Coagulation is a high risk and very much serious haemorrhagic disorder, which is potentially fatal. It is more frequently observed as a complication of obstetric disorders, diffused neoplasm, bacterial sepsis, blood transfusions (especially multiple ones), trauma and fat embolisms etc.

This author[1] has lucid recognition of the importance in the laboratory diagnosis of DIC. Whenever D-dimer and Fibrin Degradation Product (FDP) tests are available, the diagnosis can be well established using the equipment of a specialized laboratory, but it has been very difficult for the general laboratory to do so. Furthermore, it is difficult to accomplish such tests with standardised results among most of the general readership.[2] Under such circumstances it is necessary to retrospectively verify and validate the clinical significance of the results derived from the screening tests. Hence, it is necessary to evolve a set of scoring system in order to evaluate the efficacy of such a laboratory diagnosis, for example, without including D-dimer and FDP. While taking notice of patients who are having renal, hepatic and respiratory involvement along with PT and APTT alterations, under such a circumstance, it is very strongly suggestive as a diagnosis of DIC, by using merely the screening tests. Haemostatic tests like Haemoglobin (Hb), Haematocrit (HCT), Platelet Count, PT, APTT, Fibrinogen, Fibrin degradation product (FDP) and D-dimer are usually employed.

Formulation of Diagnostic Hypotheses:

1. It was hypothesized that the patients who were admitted to the intensive care unit (ICU) with proper clinically admissible diagnosis of DIC would have all fulfilled the requirements of a scoring system, even just retrospectively.
2. It was as well hypothesized that this system would have assessed the scores of Hb, HCT, APTT, and 3 screening tests, namely Platelet Count, PT, and Fibrinogen. Same system also would have assessed the score of the underlying disease, regardless of that of the confirmatory tests.
3. Regarding the confirmatory tests, it is hypothesized that it was not necessary that each of the DIC patients needed to undergo the entire spectrum of confirmatory tests.

In fact, the number of the confirmatory tests taken was not only insignificant as compared to that of the screening tests, but also the items of the confirmatory tests that were taken did vary very highly from one patient to another. Hence, the confirmatory tests were not taken into account when the scoring system was contemplated purely due to their nature and availability of being confirmatory. It was definitely not because they were regarded as less important than the screening tests, i.e., APTT, Hb, and HCT. Conversely, FDP is considered as the one test just next to D-dimer to the extent that the

diagnostic power is concerned. As the scoring system was retrospective, there was no validation needed.

MATERIAL AND METHODS

With the afore-mentioned background information of various haemostatic test results, 98 consecutive admissions to the second Surgical Intensive Care Unit (SICU), Changhua Christian Hospital Medical Centre, located in the central part of Taiwan, from January 1, 1999 to November 30, 2001 were included in the study. There were 94 patients' data suitable for this study. The remaining 4 patients' data were not used as they were not completed. There was not any pair of those 94 patients related to each other. It is noted that SICU, during that period, also accepted admission of non-surgical patients.

The criterion used to retrospectively evaluate diagnosis of DIC was the abnormal results of Hb%, HCT, Platelet Count, PT, APTT, and Fibrinogen.

Euglobin lysis time, FDP, D-dimer, and thrombin time were not included because the available number of patients who had one or more of these 4 tests were really insignificant. Such a situation was true especially during the initial stage of admission prior to entering SICU, either in the evenings or at the weekends, despite of the full understanding that the D-dimer is regarded as one of the best single test for the diagnosis of DIC. Generally speaking, PT, serum fibrinogen level, and platelet count have been suggested as components of the screening tests.[3-6] Abnormality in all of the three in the absence of liver disease or dilution due to severe blood loss is a sign of DIC.[7, 8] The screening tests included PT, serum fibrinogen level, platelet count, APTT, HCT, and Hb%. Confirmatory tests included the test for D-dimer as well as that for FDP levels, thrombin time and euglobin lysis time.[9]

As for the normal range of the platelet count, it was from 150 to 460×10^3/μl, while PT ranged from 10.6 to 12.1 seconds. A value of PT >12.1 seconds was considered as abnormal. Prolongation of PT was recorded as 1 second and 3 seconds respectively. The normal range of APTT was from 28.0 to 40.3 seconds, while that of the fibrinogen was from 200 to 535 mg/dL. Out of these 4 tests, combination of abnormality of at least any 3 of them required mandatory admissions of the potential DIC patients to SICU.

As the International Scoring System for DIC was not available until sometime during the year of 2001, therefore, our own imaginary one was constructed retrospectively. This system is as following:

- underlying diseases, each scored 2;
- 1 second prolongation of PT scored 1, while that of the 3 seconds of PT2 scored 2;
- platelet count if $<150\times10^3$/μl scored 1, while if $<137\times10^3$/μl scored 2;
- APTT >40.3 seconds scored 1; and
- the fibrinogen level if <200 mg/dL scored 1, while if <100 mg/dL scored 2.

The total score was then (2+1+1+1+1=6), while the maximal one was (2+2+2+1+2=9) (Table-1). Therefore, each patient who was admitted to the SICU at least had a minimal score of (2+1+1+1=5), within which each underlying disease constitutes a partial score of 2 (see Table 1.).

Table-1: The scoring system for DIC patients from Jan. 1999 to Nov. 2001

Characteristics	Scoring values
1 second prolongation of PT	1
3 second prolongation of PT	2
Platelet count <150 Platelet count <137	1 2
APTT>40.30	1
Fibrinogen level < 200 Fibrinogen level < 100	1 2
Full score	(2+1+1+1+1=6)
Maximum score	(2+2+2+1+2=9)
Each patient who was admitted to SICU at least had a minimal score of	(2+1+1+1=5)

Among the 94 patients, following four major groups were categorized (Figure-1):

1. Head injury,
2. Trauma other than head injury,
3. Critical medical diseases, and
4. Minor medical/gynaecological/obstetric diseases.

With regard to different age groups, following five sections were classified: >65, 50–64, 35–39, 20–34, and <20 years old.

Using SPSS version 10.0, statistical analyses were performed. A two-tailed *p* value <0.05 was recognised as significant, with the exception of where '**' is denoting significant level of 0.01. Kruskal Wallis test was used with ordinal data as well as with interval or ratio data. Spearman rank correlation coefficient was tested for only ordinal data, while Pearson correlation coefficient was applied when interval or ratio data are available.

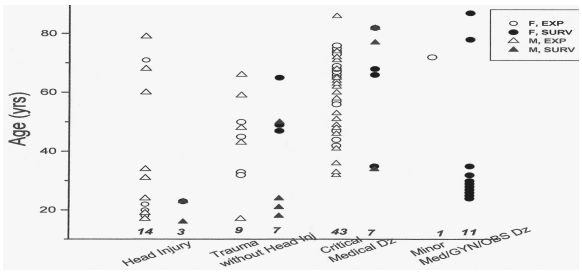


Figure-1: Four major groups of DIC patients

RESULT

Since each patient who was admitted to SICU had at least a minimal score of 5 (2+1+1+1) under this retrospective scoring system, those patients who had improved and then discharged from the SICU would have had improved (decreased) their scores, while those who expired would have had reached (increased) their scores to the full or even the maximal level, 6 or 9 respectively, immediately prior to their deaths.

Among this battery of six tests employed in this study, difference in the result of PT was significant among the five different age groups. PT valued 7,300 seconds was noted in 3 patients. Those 3 data were considered as outliers of PT distribution.

It is noted that about a half (45.679%) of our patients had plasma fibrinogen >200 mg/dL, while 22.23% had plasma fibrinogen <100 mg/dL. The serum levels of fibrinogen were valued 837.50, 569.50, 546, 497.60 mg/dL etc in descending order.

The mean value of the platelet count was $127.33\times10^3/\mu L$, and its minimal was $6.73\times10^3/\mu L$ (Table-5). Platelet counts were 640, 561, 492, 453, 422, $407\times10^3/\mu L$ etc in descending order.

The minimal Hb was 3.00 gm%, and HCT was as low as 8.79%. Among all the tests used, HCT was the one that had shown significant results starting from subnormal ranges rising up to the normal or even at times above normal ranges for those patients who had shown signs of improvement and then were discharged from the SICU. The correlation between the test results of HCT and Hb was positively strong with the Pearson's correlative coefficient being 0.834 (Table-6). Both HCT and Hb were statistically in a normal distribution respectively (Figure-2).

However, an evaluation of the correlation between age of DIC patients and their haemostatic markers revealed that, statistically, almost no correlation existed between age and PT, although the direction of such a pebble-sized correlation was positive.

Correlation between age and platelet count was minimal (with the direction in negative), while that of fibrinogen was positively minor.

The correlation coefficient between age and APTT was more than 0.2 and in a positive direction, i.e., +0.208 (Table-3). Correlations between age with PT, Platelet count, and Fibrinogen, respectively, were significant (Table-3). As for the relationship between age and serum fibrinogen level, the verified data available existed in 79 instead of 94 patients (Figure-3).

Table-2: Differences among 6 haemostatic tests for 5 different age groups.

	Hb	HCT	Plate	PT	APTT	Fibrinogen
Chi-Square	3.816	7.538	8.150	9.647	9.103	10.857
Df	4	4	4	4	4	4
Asymp. Sig.	.432	.110	.086	.047	.059	.028

By Kruskal Wallis Test, Grouping Variable, 5 different age groups

Table-3: Correlation between age of DIC patients and their haemostatic markers

Haemostatic Marker	Spearman's Correlation Coefficient
Fibrinogen	0.013
Platelet	–0. 070
APTT	0.208
PT	0.067

Among the 6 screening tests, merely HCT and Hb presented normality in their distribution respectively, while the rest of 4 are in non-normal distribution. Other than Hb and HCT, the skewness and kurtosis measures of the rest of 4 tests ranged from A to B as following:

A:

Skewness Measure Value	Kurtosis Measure Value
8.897316e+6	1.406687e+10

B:

Skewness Measure	Kurtosis Measure
613658.216150	7.357498e+9

The outcome of those patients revealed that in the first major group of the head trauma, 14 patients expired, and the other 3 patients showed signs of improvement. In the second major group of traumas other than head injury, 9 patients expired, and the other 7 patients improved.

Table of Correlation between various parameters

			Age	PLATE	PT	APTT	Fibrinogen
Spaerman's rho	AGE	Correlation Coefficient	1.000	-0.070	0.067	0.208	0.013
		Sig. (2-tailed)		0.506	0.536	0.066	0.906
		N	94	93	88	79	79
	PT	Correlation Coefficient	0.067	-0.346**	1.000	.744**	-.561**
		Sig. (2-tailed)	0.536	0.001		.000	.000
		N	88	89	94	78	79
	APTT	Correlation Coefficient	0.208	-0.392**	0.744**	1.000	-.404
		Sig. (2-tailed)	0.066	0.000	0.000	.	.000
		N	79	80	78	80	78
	Fibrinogen	Correlation Coefficient	0.013	0.277*	-0.561**	-0.404	1.000
		Sig. (2-tailed)	0.906	0.013	0.000	0.000	
		N	79	80	79	78	80

*Denote that at the significant level of 0.05 (2 tailed), the correlation is significant. ** Denote that at the significant level of 0.01 (2 tailed), the correlation is significant.
** Correlation is significant at the 0.01 level (2-tailed), * Correlation is significant at the 0.05 level (2-tailed)

Figure-2: Histograms of Haemoglobin

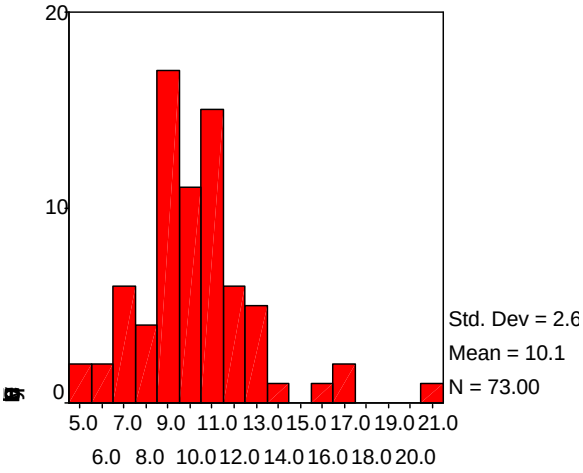


Table-4: Comparison of DIC patient distribution in percentage between Wada *et al*'s and Tang's studies, according to the different plasma levels of Fibrinogen.

% of patients distribution in different studies	<16 mg/dL	<100 mg/dL	>200 mg/dL
Tang's study(current)	1.231%	22.222%	45.67%
Wada *et al*'s study *	-	24%	47%

* Denotes the source of reference (33, Wada et al, 2003).

Table-5: Mean, maximum and minimum values of haemostatic markers

Biomarkers	Mean	Minimum	Maximum
Hb	9.7617±2.83447	3.00	21.00
HCT	27.834±7.88375	8.9	49.70
Platelet	127.33±128.1445 *	6.73	640.00
PT	265.42±1307.26 #	9.80	7300.00
APTT	63.235±46.334913	25.00	267.80
Fibrinogen	225.048±151.605373^	15.00	837.50

*Platelet counts have the following values in descending order: 640, 561,492, 453, 422, and 407 etc. #PT was 7,300 seconds in 3 patients. ^Serum levels of Fibrinogen had following values in descending order: 837.50, 569.50, 546, 497.60 mg/dL etc.

Descriptive Statistics for Prothrombin Time (PT)

	N	Minimum	Maximum	Mean	SD
PT seconds	89	9.8 Sec.	7300.0 Sec.	265.428 Sec.	1321.438
New PT	86	9.8	150	20.0360	19.1541

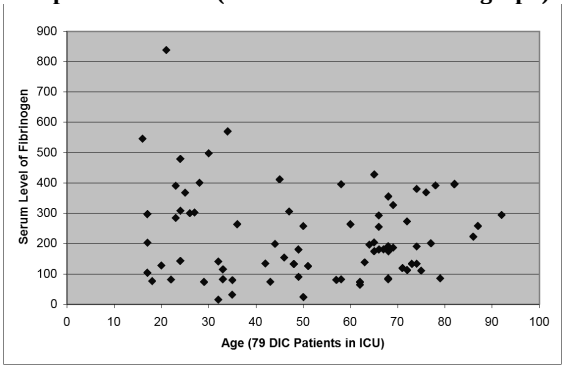
Table-6: Comparison of means and minimums, and the correlation of test results between HCT and HB

Test results		Mean	Minimum	Pearson' correlation coefficient
HCT		27.834	8.90	
HB		9.7617	3.00	0.8343627*
			Hb	HCT
Hb	Pearson's Correlation		1.000	0.834*
	Significance (two tailed)			0.000
	Case number		94	94
HCT	Pearson's Correlation		0.834**	1.000
	Significance (two tailed)		0.000	
	Case number		94	94

*at the significant level of 0.05 (2-tailed), the correlation is significant.
**at the significant level of 0.01 (2-tailed), the correlation is significant.

In the third major group of critical medical diseases, 43 patients expired, and the other 7 patients improved in their health. In the fourth and final major group of minor medical/gynaecological/obstetric diseases, only one patient expired, and the rest of 10 patients improved (Figure-1). Totally, 67 patients eventually expired after their stay in the second SICU. Mortality rate was 71.27 %.

Figure-3: Correlation between Age and Serum level in DIC patients in ICU (79 case were used in this graph)



(Verified data available from 79 patients)
Kruskal-Wallis test the *p* values of both prothrombin time and fibrinogen are significant.

DISCUSSION

A brief review of the mechanism of fibrinolysis may help to understand the issues, which we shall advance later in an attempt to explain the characteristics and pitfalls of laboratory diagnoses. Fibrinolysis in the humans is an important homeostatic process,[1,2,7] and serves primarily to limit the fibrin deposition. Fibrinolysis is mediated by plasmin. This enzyme is present in the blood and other body fluids in the form of plasminogen. There are activators activate plasminogen. Of particular significance is the observation of Moltke[3] that large quantities of the plasminogen activator are present in the leptomeninges of the brain. Important interactions have been demonstrated among the major haemostatic systems in humans.[4-6] With regards to fibrinolysis, both the thrombin and kallikrein have been found to be plasminogen activators. The fibrinolytic disorders may result from either the primary activation of the fibrinolytic system or by a secondary activation of this system as a consequence of the intravascular coagulation.[6-16]

Although DIC has been intensively studied during the last 35 or more years,[17-25] the mechanism of several clinical problems of DIC is unclear. It has been very difficult for the general laboratory to accomplish tests just as a specialized laboratory does with standardised results. It may be worthwhile to discuss some haemostatic tests, which have been commonly used in ICU, with their diagnostic characteristics and pitfalls.

Bacterial infection, in particular, septicaemia, is the most common one associated with DIC.[26-28] The laboratory findings revealed that almost all of the DIC patients had a mild leucocytosis, reduced haematocrit, thrombocytopenia and hypoalbuminemia.[29] Cytokines were mainly produced by the activated mononuclear cells in response to the triggers of the microorganism's endotoxin and bacterial exotoxins.[30,31]

Severe trauma is another clinical condition frequently associated with DIC.[32] Systemic cytokine conditions were basically identical in patients with injuries and those with sepsis.[25] For the head injury patients in particular, due to the large amount of tissue factor presents inside the central nervous system, both the cerebral and systemic coagulation activations have to be taken into account.[6,23]

Among the DIC patients with the cause of head trauma, such as in the first major group of our study, it is important to refer to Moltke's findings.[3] He demonstrates large amounts of plasminogen activators in the leptomeninges of brain. Sicuteri *et al*,[16] along with Tang[23] demonstrated that the kallikrein-kinin system is activated by subarachnoid haemorrhage. This activation is accomplished when the blood is diluted by the cerebrospinal fluid. The formation of kallikrein would then constitute a second mechanism favouring the plasmin activation.[17-20,23]

Serum fibrinogen level measures the amount of fibrinogen in the serum, but also suggests the extent of depletion of clotting factors, hence, is of prognostic significance.[11,12] It also guides therapy. Levels of >150 mg/dL occur in about 70% of patients with DIC.[19] On the contrary, with respect to the high plasma fibrinogen test level, such as a part of observation in this study, why such an event has been sometimes paradoxically encountered in the poor clinical outcome of DIC patients? As reported in the section of Results, the 45.679% of our patients had >200 mg/dL of the plasma fibrinogen, while the other 22.23% had <100 mg/dL of the plasma fibrinogen (Table-4). It indicated that the plasma fibrinogen level is likely not a sensitive marker for DIC. Note that Wada H. *et al* also measured the plasma level of fibrinogen in their 560 patients of DIC, the size of their patients' cohort was coincidentally 5 times exactly of that of the current study.[33] They also evaluated the relationship between the fibrinogen and the outcome of their patients, and compared the correlation between the fibrinogen with other haemostatic markers. Forty-seven percent of their patients had >200 mg/dL of plasma fibrinogen and 24% had <100 mg/dL of plasma fibrinogen. This consistency further supports this author's contention that plasma fibrinogen level is not a sensitive marker in any practical manner for the laboratory diagnosis of DIC (Table-4, Figure-3).

Platelet count more accurately reflects the extent of platelet depletion. Counts of less than 1,000,000/mm^3 are found in about 90% of cases.[9,26]

Thrombocytopenia may conversely be evident on peripheral smear—each platelet seen in an oil immersion field (1,000×) corresponds to a count of 10,000 platelets/mm^3. Schistocytes or fragmented red blood cells may be seen in 50% of cases and indicates microcirculatory thrombosis.[21-23] The minimum value of the platelet count among our 94 patients was as low as $6.73\times10^3/\mu L$ (Table-5). Occasionally, patients had bone marrow examination and were diagnosed with the paucity of megakaryocytic. This would indicate that the low platelet count was primarily related to the lack of platelet production rather than to the platelet consumption. It is noted that bone marrow examination is not a routine examination for DIC patients. Nevertheless, the low platelet counts alone is not sufficiently nor necessarily to be correlated with the poor outcome of the DIC patients, as noted in some of patients in the third major group of critical medical diseases.

The prothrombin time tests the extrinsic pathway and is abnormal in over 90% of patients with decompensated DIC.[7,26] It is also prolonged in liver disease but may be normal in mild or compensated DIC.[13] The partial thromboplastin time, like the whole blood clotting time, tests the integrity of the intrinsic pathway. It is particularly sensitive to deficiencies of factors IX and VIII.[13] Being more sensitive than whole blood clotting time, it is prolonged in a majority of cases of decompensated DIC.[33]

With regard to the test results of both the PT and APTT, although the hypercoagulable states are most often associated with venous thrombosis, it is note that the arterial thromboses are also reported in antithrombin III deficiencies, the factor V Leiden and prothrombin gene mutations, the dysfibrinogenemia, plasminogen deficiency, the hyperhomocysteinemia, the sickle cell disease, and the antiphospholipid antibody syndrome.[36,37]

It is noticed that patients affected with the Haemorrhagic syndrome caused by contact with caterpillars of the *Lonomia* genus shows multiple systems bleeding with haematoma, haematuria and ecchymosis. The treatment with whole blood or fresh frozen plasma worsens the clinical picture and causing a severe drop in the platelet count often resulting in the renal failure and death. This syndrome is caused by a mild DIC in combination with a hyperfibrinolytic state. Additionally, the mild DIC is being partially obscured by the hyperfibrinolytic condition.[38]

The 1-second prolongation of PT took place in 59 patients, while that of 3 second occurred in 45

patients. In fact, any prolongation of PT is the sentinel event of a dilutional coagulopathy and does occur early in its stage. The key to prevent such a coagulopathy is to have the plasma infusion before PT becomes sub-haemostatic. A concurrent transfusion of plasma with blood is another effective strategy for minimizing the coagulopathy with the presence of the prolonged prothrombin time,[39,44] unfortunately, the existing protocols underestimate the dilution of clotting factors in severely bleeding patients.

History taking has been an important measure in managing DIC patients, for example, the patients' medical history of taking products such as phenprocoumon merits our attention. The total and unbound plasma concentrations of phenprocoumon and the prothrombin complex activity merit consideration. Such concentrations were calculated in a study of 51 patients on phenprocoumon. A 7-time distinction in the dosing rate (10–70 μg/kg/day) was needed to sustain the prothrombin complex activity about 10 to 30% of normal.[55] The disparity in dosing requirement was basically due to inter-individual differences in the intrinsic clearance of phenprocoumon and merely to a minor degree to differences in sensitivity to it. On average patients with myocardial infarction required only 2/3 of the daily dose of phenprocoumon of post cardiac surgery patients and patients with thrombosis and emboli, not to mention DIC. That difference seemed to be due to higher clearance in surgical patients and to greater resistance to phenprocoumon in patients with thrombosis and emboli to the extent that DIC patients are concerned.[55] Of importance in this context as well lays on the fact that DIC patients are particularly needed to be evaluated and taken into serious consideration in the correlation between prothrombin time and factors responsible for inter-individual differences in the prothrombin complex activity. Among those factors, age is one of the most important variables that are required to be taken in account. The total clearance of medications such as phenprocoumon in individuals (patients) differed about 5-time. It was better forecasted by the inter-individual intrinsic clearance (r=0.84) than by the unbound fraction of plasma concentrations of phenprocoumon (r=0.15).

Although the coincidence of DIC and leukaemia is well known as one of the critical medical disease, and as well as the association between pyoderma gangrenosum (PG) and leukaemia, a premonitory effect of PG in the combination with the DIC preceding the diagnosis of chronic myelomonocytic leukaemia in the same case has not been reported until recently.[40] The coagulopathy with consequently abnormal haemostatic tests have well explained it.

As in the current study, the collection of clinical data were traced back to January 2, 1999, clinically, at that time we did not have any benefit to start using the Biphasic APTT waveform. However, it is interesting and important to know whether the presence of it is associated with any adverse clinical outcome or not among patients outside from an ICU. Smith et al reported that the consecutive patients from the emergency department or the non-ICU inpatient wards with a BPW were enrolled prospectively, along those patients with a BPW would have a significantly longer hospital stay, were more likely to have a positive growth in the microbial culture, were transferred more often to an intensive care unit, and were more likely to receive a red blood cell transfusion.[41] Among those patients, those who came from the emergency department with a BPW were more likely to be admitted to the hospital as inpatients in the ensuring future. Those results indicate that the BPW is associated with an increased rate of adverse events among the non-ICU patients.[42] Toh, Samis, Downey et al. reported that the degree of this change on patients' admission to the hospital and their study predicts the DIC better than to use the D-dimer measurements.[43]

For PT, the standardization of reagents and method is not established yet for any universal purpose except the International Normalized Ratio (INR) for the control of oral anticoagulant therapy (OAT).[45] There is a potentiality to introduce the INR system to the diagnosis of DIC when the human TF is used as a PT reagent.

Any vascular lesion, such as Kasabach-Merritt syndromes (KMS) [45-48] has to be taken into consideration for the association with DIC. The relation between the blood flow pattern in the abdominal aortic aneurysm (AAA) and DIC characterizes by FDP-D-dimer (FDP-DD) or the thrombin-antithrombin complex (TAT). Mitasuoka *et al*'s findings[44] suggest a close link between the abnormal blood flow pattern in AAA and the activation of the coagulation-fibrinolysis system.[46]

The original KMS reported in 1940 is currently known to have been related with kaposiform hemangioendothelioma and thrombocytopenia. Such vascular lesion activates intravascular coagulation with platelet trapping and activation, along with the consumption of coagulation factors.

As of Spring 2008, true pathogenesis of coagulation system disturbances of cancer patients is still very poorly understood.[51-53] The disordered coagulation is encountered in up to about 90% of the cancer patients, although only 15% of them develop a localized acute or chronic deep venous thrombosis or a DIC.[35] The elevated levels of D-dimer and soluble fibrin are very sensitive for the diagnosis of DIC in such patients, and a normal level has a high negative predictive value.

In fact, the correlation between test results of the HCT and HB did appear positively strong with

the Pearson's coefficient being 0.834 (see Tables 5, 7 and Figure-4), in light of the moderate sample size in the current study.

Table-7: Correlation between Haematocrit and Haemoglobin of DIC patients in ICU

Test results	Mean	Minimum	Pearson's correlation coefficient
Haematocrit	27.834	8.90	0.834
Haemoglobin	9.7617	3.00	0.834

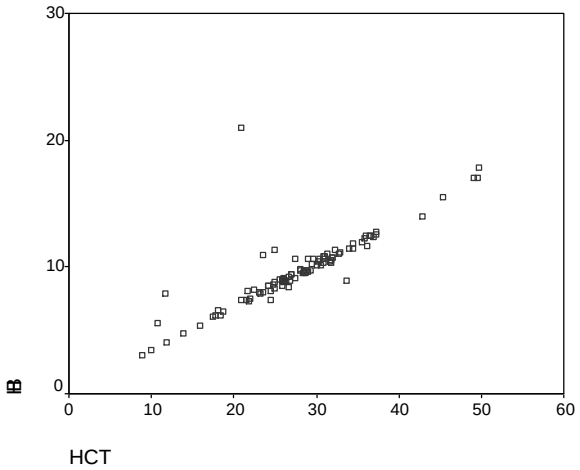


Figure-4: Correlation between HCT and Hb in DIC patients

The straight line denotes statistically very strongcorrelation in positive direction.

HCT test was the one and only one that was taken as frequently as 6 or more times during the SICU stay of all the 94 patients. The decrease in the value of the HCT tests in the current study reflected the continuous destruction of red blood cells, the continuous blood loss, or both, and may resulted in hypovolemia. A delay in the correction of hypovolemia, a postponement in the diagnosis and treatment of the defective coagulation, and a deferring in any surgical control of the bleeding are the avoidable factors in most deaths caused by haemorrhages with the surgical and obstetric lesions. In patients of this study with the obstetric crises, the degree of hypotension was the first guide to the level of blood loss, except in the abruptio placentae. A protocol incorporating the guidelines should be strictly followed. The serial monitoring of the response to treatment is essential.

Patients with the systemic impairment and multiple organ failure, along with the PT and APTT changes were very strongly suggesting the diagnosis of DIC, despite of lack of the D-dimer and/or FDP in establishing such a diagnosis.

Such as in the current study, the DIC may then be interpreted as the real underlying cause of these numerous clinical pathologies.

This author with his two co-authors published *Primary Fibrinolytic Syndrome Associated With Subarachniod Haemorrhage*.[56] In addition, in 1999, this author revisited this issue, and contributed a chapter in *Neurotraumatology*[23] published by Monduzzi Editore, Italy. Such a correlation has not been previously reported.

CONCLUSION

The authors of *Primary Fibrinolytic Syndrome Associated With Subarachniod Haemorrhage*[56] strongly suggest that subjects with subarachnoid haemorrhage should be evaluated for increased systemic fibrinolytic activity as a part of routine haemostatic workup. Beyond the debate of mechanism of DIC arising whether from primary or secondary fibrinolytic syndrome, the association of Subarachnoid Haemorrhage with DIC deserves our immediate attention. With regard to the roles of age and gender, the nutritional status of the patients upon their admission to the SICU, the exactly chronological time of drawing patients' blood, the therapeutic time of transfusion, especially that for the transfusion of fibrinogen, and the details of improvement of the patients' DIC scores for those who have survived, all these would certainly be significant factors, and warrant further evaluation. This author highly considers employing the International Scoring System for the diagnosis of DIC, which was not published until sometime in 2001[19], almost two years after the first patient of this study admitted to SICU. Nevertheless, this author is confident to summarize with the following 14 points of impression with significance:

1. The high plasma fibrinogen test level sometimes encounters in the poor clinical outcome in DIC patients.
2. The low platelet count alone is not sufficiently nor necessarily to be correlated with the poor outcome of DIC patients.
3. The arterial thrombosis clinically presents with the manifestation of coagulopathy and arterial stroke.
4. In case of the DIC patients affected with haemorrhagic syndrome, who clinically manifest with bleeding from multiple organs, it is important to ascertain whether the treatment with whole blood or fresh frozen plasma may worsen the clinical picture or not. Since this type of syndrome is caused by a mild DIC in combination with a hyperfibrinolytic state, it is crucial to recognize if the former (DIC) being partially obscured or not by the latter (hyperfibrinolytic state).
5. The key to prevent a coagulopathy is the plasma infusion before the prothrombin time becomes sub-haemostatic.

6. The biphasic APTT waveform can be used to determine the onset of DIC. It is a potential predictor and novel marker of the impending DIC.
7. There is a potentiality to introduce the INR (International Normalized Ratio) system to the diagnosis of DIC when human tissue factor is used as a PT reagent.
8. The fragmented red cells, thrombocytopenia and elevated D-dimers do not always indicate the existence of a DIC, even in the presence of a bleeding tendency.
9. For some cancer patients, it is important to be aware that a haemostatic imbalance may be detected toward a primary fibrinolysis in the preoperative period, while the low grade DIC could be observed postoperatively.
10. HCT and HB are still important for managing the DIC patients, especially when they are in a hypovolaemic condition.
11. The elevated levels of D-dimer and soluble fibrin are very sensitive for the diagnosis of DIC in cancer patients, and a normal level has a highly negative predictive value.
12. The diagnosis for DIC can be well established using the equipment of a specialized laboratory, but as for patients with the systemic impairment and multiple organ failure, along with PT and APTT changes, is very strongly suggesting DIC, even in the absence of the result of D-dimer and/or FDP.
13. Estimation of individual clotting factor or antithrombin III levels is rarely required in the clinical practice.
14. The diagnosis of *Primary Fibrinolytic Syndrome*[56] has to be kept in mind upon any further difficulty in establishing the differential diagnosis for DIC, especially upon the situation of subarachnoid haemorrhage.

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