

Diagnostic Criteria and Laboratory Tests for Disseminated Intravascular Coagulation

Toshihiro Kaneko¹⁾ and Hideo Wada²⁾

Disseminated intravascular coagulation (DIC) is associated with organ failure and it is often fatal condition. The main underlying diseases are infection, hematological malignancy and solid cancer. DIC is subclassified into overt DIC and non-overt DIC. The International Society on Thrombosis and Haemostasis (ISTH) and the Japanese Association for Acute Medicine (JAAM) published the diagnostic criteria for DIC after several recent clinical trials. These diagnostic criteria are modified versions of the Japanese Ministry of Health, Labor and Welfare (JMHLW) criteria. The JAAM diagnostic criteria demonstrated excellent sensitivity for mortality but low specificity. The mechanisms of onset of DIC vary based on the underlying diseases, and depend on tissue factor, cytokines, etc. Early diagnosis and early treatment for DIC are important, and the use of hemostatic molecular markers is necessary to successfully make an early and rapid diagnosis. The mortality of DIC might be improved by the administration of recombinant activated protein C or recombinant thrombomodulin. Further investigation to improve the mortality of DIC is required, including new methods for diagnosing and treating the disease. [*J Clin Exp Hematopathol* 51(2) : 67-76, 2011]

Keywords: disseminated intravascular coagulation (DIC), diagnostic criteria, hemostatic molecular marker

INTRODUCTION

The Japanese Ministry of Health, Labor and Welfare (JMHLW), the International Society on Thrombosis and Haemostasis (ISTH) and the Japanese Association for Acute Medicine (JAAM) have recommended diagnostic criteria for disseminated intravascular coagulation (DIC).¹⁻⁴

The expression “death is coming” was used to reflect the severity of DIC as a disease with a poor prognosis. The diagnosis and treatment of DIC are therefore important and an early diagnosis of DIC as pre-DIC may help improve the patient survival. Recent clinical trials conducted using anti-thrombin (AT)⁵ and recombinant activated protein C (APC)⁶ in cases of severe sepsis, and using recombinant thrombomodulin (TM)⁷ in subjects with DIC, showed that the drugs had therapeutic effects against DIC. DIC may therefore eventually be considered a condition that can be treated effectively with anticoagulant therapy, instead of a disease with a poor prognosis.

DEFINITION

The definition of DIC differs depending on whether the term is used by a clinician, a laboratory technologist, a research scientist, an official of the JMHLW or a person working in the private sector. It can also vary depending on the social infrastructure, geographical location, economic condition, level of health care, the history of research on DIC, etc. The earliest definition and concept of DIC required evidence of the presence of microthrombi and it emphasized the prominent hemorrhagic tendency caused by consumptive coagulopathy due to the formation of multiple microthrombi. Since this early definition, the concept of DIC has undergone changes, as new types of cases were discovered and advances were made in research. It is now clear that it is difficult to directly prove the presence of microthrombi in many DIC cases, therefore the results from clinical laboratory tests are used instead. In addition, symptoms of organ failure are now considered to be more important than hemorrhagic symptoms.

The DIC diagnostic criteria established by the JMHLW¹ are not based on any definitive definition or concept. These criteria were prepared to cover the hemostatic abnormalities in a large number of typical DIC cases that were reviewed by specialists in DIC. Müller-Berghaus *et al.* proposed the concept of disseminated intravascular fibrin formation, and attempted to diagnose DIC based on the increase in soluble fibrin (SF).⁸ However, their proposal was not adopted by the

Received : April 19, 2011

Accepted : April 23, 2011

¹⁾Department of Patient Safety and Infection Control and ²⁾Molecular and Laboratory Medicine, Mie University Graduate School of Medicine, Tsu, Japan

Address correspondence and reprint request to A/Prof. Hideo Wada, M.D., Department of Molecular and Laboratory Medicine, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu-city, Mie-ken 514-8507, Japan

E-mail : wadahide@clin.medic.mie-u.ac.jp

ISTH because measurement of SF was not widely practiced at that time, and it could not be confirmed that the increase in SF was specific to DIC. The Scientific and Standardization Committee (SSC) of the ISTH (SSC/ISTH), in its meeting held in Paris in 2001, proposed defining DIC as shown in Table 1. The SSC ignored consumptive coagulopathy and the presence of clinical symptoms. The evidence required for microthrombi formation was replaced by that of intravascular fibrin formation, and vascular endothelial cell damage was recognized as an important condition related to DIC. It was also accepted that organ symptoms were no longer solely caused by thrombi but also by hyperendotoxemia and hyper-cytokinemias in the blood. With this definition, the SSC/ISTH confirmed the importance of fibrin-related products in DIC. It was suggested that DIC has two main mechanisms of onset, one non-inflammatory and the other inflammatory. The non-inflammatory DIC is seen in patients with leukemia or aortic aneurysms while inflammatory DIC is found in patients with sepsis or collagen diseases. The SSC/ISTH also proposed to divide DIC conditions into overt-DIC, where the hemostatic

system is in a decompensated state, and non-overt DIC (pre-DIC), where the system is in a compensated state. The initial definition and concept of DIC were proposed based on its pathology, but now, with more cases being studied and new developments in testing methods, there has been a gradual shift to clinical laboratory test-based definitions. It is likely that in the future, this definition will be based on evidence of new DIC therapy and disease prognosis. For now, the definition/concept of DIC proposed by the SSC/ISTH seems to be the most appropriate, but this definition/concept can probably be improved, and will likely continue to change as research progresses.

DISEASES UNDERLYING DIC

DIC can result from an underlying disease which may not always be diagnosed. The 1998 survey by the JMHW showed that underlying diseases with high incidence of DIC include hematopoietic tumors like acute promyelocytic leukemia (APL) and acute myeloblastic leukemia, obstetric diseases like placenta previa and amniotic fluid embolism, fulminant hepatitis, etc (Table 2).⁹ The underlying diseases with a high incidence of absolute numbers of patients with DIC include infections like sepsis, shock, solid tumors like hepatic and gastric cancers, and non-Hodgkin's lymphoma. A recent prospective study showed a high incidence of DIC in patients with infections, solid tumors, hematopoietic tumors, and aortic aneurysm (Table 3).¹⁰ Early reports of DIC suggested that the highest incidence was reported for obstetric diseases, followed by leukemia. Recently, the JAAM diagnostic criteria³ and DIC treatment guidelines¹¹ that focused on infectious DIC with high absolute numbers have been published. With the aging and improvement in the 5-year survival rate of

Table 1. The SSC/ISTH definition and concept of disseminated intravascular coagulation (DIC)¹

<p>Definition : DIC is an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction.</p> <p>Concept : DIC is a disease characterized by the generation of fibrin related products (SF, FDP, D-dimer, etc) and acquired (inflammatory) or non-inflammatory disorder of the microvasculature that occur in response to the formation of the fibrin-related products.</p> <p>DIC is divided into two disease stages, overt-DIC (decompensated DIC) and non-overt DIC (compensated DIC)</p>

Table 2. The underlying diseases associated with disseminated intravascular coagulation (DIC) based on a report by the Japanese Ministry of Health and Welfare in 1998

High absolute number	High frequency number	Underlying disease	DIC	Total	Frequency
1	3	Sepsis	166	410	40.5%
2		Non Hodgkin's lymphoma	154	777	19.8%
3		Hepatoma	113	3,545	3.2%
4	5	Acute myeloblastic leukemia	91	288	31.6%
5		Lung cancer	82	1,026	8.0%
6		Respiratory infections	78	1,205	6.5%
7		Liver cirrhosis	72	3,335	2.2%
8	1	Acute promyelocytic leukemia	71	91	78.0%
9		Gastric cancer	46	1,090	4.2%
10	6	Acute lymphoblastic leukemia	45	151	29.8%
	8	Other	33	124	26.6%
	2	Fulminant hepatitis	29	64	45.3%
	9	Chronic myelocytic leukemia	22	84	26.2%
	7	Acute myelomonoblastic leukemia	11	40	27.5%
	10	Acute monoblastic leukemia	7	28	25.0%
	4	Breast cancer	7	19	36.8%

Table 3. The frequency of the diagnosis of patients⁸

Diagnosis	Without DIC	With DIC	Pre-DIC	total
Infectious disease	142	71	6	219
Solid cancer	81	50	11	142
Hematopoietic tumor	54	49	11	114
Aneurysm	14	14	1	29
Obstetrics disease	4	6	0	10
Trauma	16	8	2	26
Digestive disease	13	5	0	18
Collagen disease	9	1	0	10
Other disease	35	7	3	45
Total	368	211	34	613

DIC, disseminated intravascular coagulation

solid tumor patients, there has been an increase in solid tumor-associated DIC cases that need to be investigated.

MECHANISM RESPONSIBLE FOR THE ONSET OF DIC

DIC is a condition caused by continuous activation of the coagulation and fibrinolysis systems within blood vessels due to an increase in “offense factors” or a decrease in “defense factors” (described below). Recently, organ dysfunction has been considered to be more important, and offense factors have been drawing greater attention. Fig. 1 shows the mechanism of onset of DIC in patients with malignant tumors and infectious diseases.

Inducers

1) Tissue factors

Leukemia, obstetric and gynecological diseases are conditions in which DIC results from the direct release of tissue factor (TF), because of large amounts of TF, which are present in leukemic cells¹² and the placenta, are released into the systemic circulation. TF rapidly activates blood coagulation factor VII (FVII) in the extrinsic pathway, TF/activated FVII (FVIIa) which activates FX to FXa, thereby producing a large amount of thrombin in the blood. Thrombin converts fibrinogen into fibrin, and simultaneously acts on protease activated receptors (PARs) on various cells by sending signals into the cells. The formation of large amounts of fibrin causes thrombosis and consumptive coagulopathy. When there is tissue collapse or monocyte activation, TF activity in the blood increases markedly. It is believed that in solid tumors, the TF released from the cancer cells and the immunological reactions to solid tumors enhances TF production from monocytes. In patients with infections, the increase in TF production plays a major role in the onset of DIC. Animal models for DIC, as described below, have been reported.

As anti-TF antibody,¹³ TF pathway inhibitor (TFPI),¹⁴ and active site inhibited FVIIa¹⁵ decreased the mortality in *E. coli*-induced DIC models. Although the TF and TFPI concentrations in the blood change with the clinical progression of DIC,¹⁶ their concentrations do not always correlate with the condition of the DIC. Tumor cells and tissues such as the placenta, also contain various substances other than TF that can affect the hemostatic system. For example, tissue-type plasminogen activator (t-PA) present in melanoma can significantly activate fibrinolysis, and cause fibrinolysis dominant DIC, together with TF and other factors.

2) Chemical mediators

During the activation of leukocytes and induction of vascular endothelial cell damage, chemical mediators play a major role in the onset and progression of DIC, as suggested from results of clinical studies and animal experiments.¹⁷ Sepsis, burns, trauma and major surgery, etc can activate blood cells and vascular endothelial cells, and lead to the production and release of chemical mediators such as tumor necrosis factor (TNF) and interleukin-1 (IL-1). The release of endotoxins (LPS) by gram-negative bacteria, especially in cases of sepsis, and peptidoglycans by gram-positive bacteria, can activate the transcription factor NF κ B (nuclear factor κ -B) via toll-like receptors (TLRs) and CD14 of macrophages to produce cytokines.^{18,19} In an LPS-induced model, inflammatory responses, such as an increase in cytokines, elastase and CRP, were seen.²⁰ In sepsis cases, where are high LPS levels, there is also a high incidence of DIC complications. There was also greater suppression of the fibrinolytic system and greater enhancement of organ dysfunction by hypercytokinemia observed in a LPS-induced rat DIC model than in a TF-induced rat DIC model.²¹

A mechanism for tissue damage by neutrophil elastase released from activated neutrophils has been proposed,²² and a close link between neutrophil infiltration and the pathological condition was demonstrated in a rat lung injury model.²³

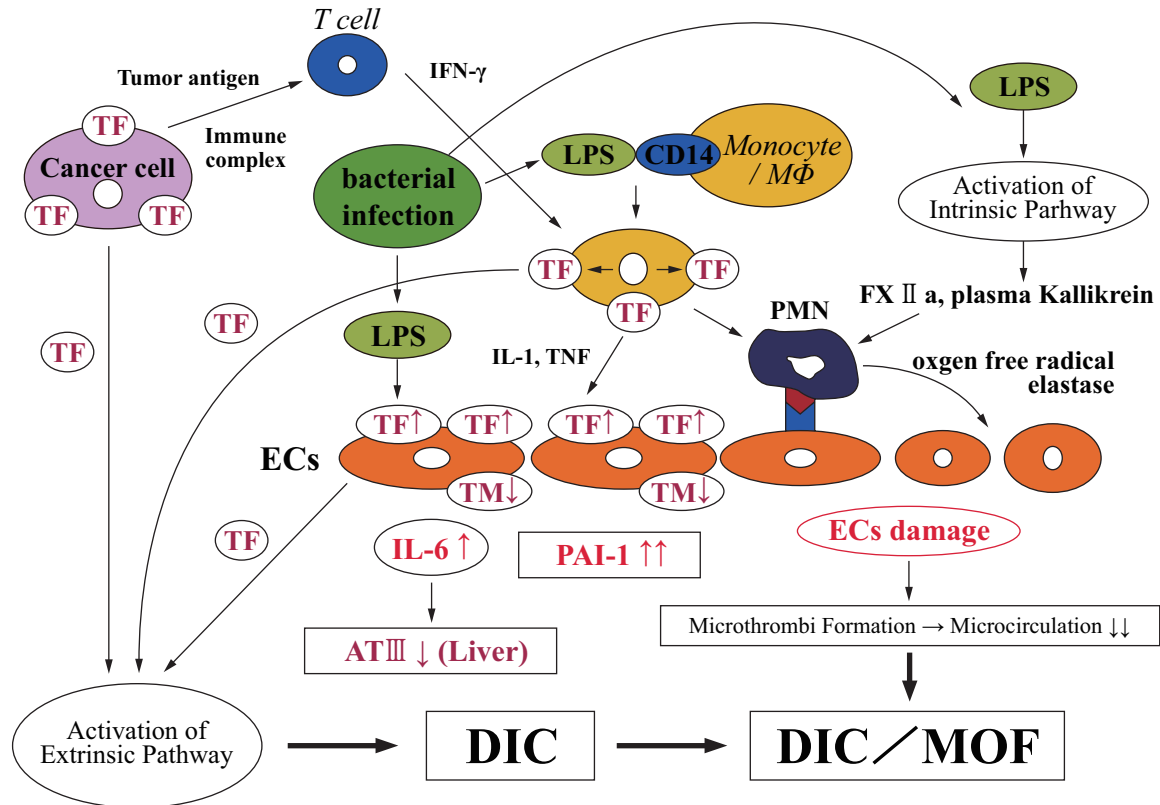


Fig. 1. The mechanism of onset of disseminated intravascular coagulation (DIC) in patients with malignant tumors and infectious diseases. AT III, antithrombin III; ECs, endothelial cells; IFN- γ , interferon; IL-6, interleukin-6; LPS, lipopolysaccharide; MOF, multiple organ failure; PAI-1, plasminogen activator inhibitor-1; PMN, polymorphonuclear cell; TF, tissue factor; TM, thrombomodulin

Microcirculatory disturbance often occurs as a result of these processes, and it leads to the further releases of various chemical mediators, leading to the development of DIC and multiple organ failure (MOF). The pathological state of systemic inflammatory response syndrome (SIRS)²⁴ is accompanied with high hypercytokinemia, and when SIRS continues for more than 3 days, the incidence of DIC is high.²⁵ The blood cytokine levels are markedly elevated in sepsis patients, and the administration of exogenous TNF or IL-1 lead to the development of a condition similar to septic shock in an animal model. Thrombin acts on PARs and activates NF κ B,²⁶ thereby enhancing the inflammatory response.

Defense factors

Protein C (PC), AT, TM, protein S (PS), TFPI, and plasmin inhibitor (PI) are known as the biological protease inhibitors that inhibit activated coagulation factors or fibrinolytic factors. A lack of these inhibitors favors the onset or worsening of DIC. Fibrinogen, acting as a substrate for thrombin, ultimately localizes the action of thrombin. In a clinical trial,

the administration of APC⁶ caused a significant reduction in IL-6, while addition of high-dose AT suppressed the effect of LPS on promoting IL-6 production by monocytes,²⁷ suggesting that APC and AT possess anti-inflammatory effect, as well as anticoagulant effects. In a sepsis-related DIC model where *E. coli* was injected into baboons, the administration of anti-endothelial PC receptor (EPCR) antibodies caused a poor outcome in all of the baboons, and their tissues showed infiltration of neutrophils,²⁸ suggesting that the PC-EPCR system has an important anti-inflammatory action.

AT, EPCR, APC, and TM also directly or indirectly prevent thrombin from acting on PAR, and thus suppressed the inflammatory response by inhibiting the activation of NF κ B. When the ability to process bacterial toxins or activated coagulation factors in the reticuloendothelial system decreases due to liver cirrhosis, anticancer agents, or tumors of the reticuloendothelial system, then these conditions are also favorable for the onset of DIC.

The fibrinolytic system prevents the development of ischemic conditions by dissolving the thrombi that were formed. When this system is weakened, and its capacity to

dissolve microthrombi is decreased, organ dysfunction develops and irreversible damage can occur. In addition, there is often an insufficient increase of blood fibrin/fibrinogen degradation products (FDP), and a markedly increased fibrinogen level in the patients with hypofibrinolysis. In patients with aortic aneurysms, cardiac arrest, angiomas, etc, thrombus formation occurs due to abnormal blood flow, and DIC develops as a result of the formation of these thrombi and fibrinolysis.

DIAGNOSTIC CRITERIA FOR DIC

Ideally, one set of diagnostic criteria for DIC should be prepared for each underlying disease. However, this would require several dozen sets of DIC diagnostic criteria which would be impractical for busy clinicians to adopt. The current diagnostic criteria in use were therefore prepared by combining the common features of the different types of DIC. The current widely used diagnostic criteria for DIC are not actually diagnostic criteria, but rather criteria for starting DIC treatment. The SSC/ISTH divided the state of DIC into overt-DIC and non-overt DIC (pre-DIC). The JMHLW DIC diagnostic and ISTH overt-DIC diagnostic criteria are both applicable for overt-DIC, while the ISTH non-overt DIC diagnostic criteria and JAAM criteria for acute phase DIC apply to non-overt DIC. Table 4 gives three sets of diagnostic criteria for DIC.

Diagnostic criteria for overt-DIC

The diagnostic criteria of the ISTH for overt-DIC² are a modified version of the JMHLW DIC diagnostic criteria^{1,29} with some differences between the two criteria. In a study

that compared the JMHLW and ISTH DIC diagnostic criteria,³⁰ concordance in DIC diagnosis was observed at 64.7% for the leukemia group and at 71.3% for the non-leukemia group. The concordance in ruling out DIC was 95.9% in the leukemia group and 99.2% in the non-leukemia group, suggesting that the ISTH overt-DIC diagnostic criteria have a higher specificity, but lower sensitivity, than the JMHLW criteria. Although the JMHLW diagnostic criteria adopted hemostatic molecular markers as auxiliary diagnostic parameters, these are not clinically used due to the cost and time involved in their measurements. The ISTH overt-DIC diagnostic criteria allow for a diagnosis of DIC even when there are no clinical symptoms, as long as there are abnormal laboratory values caused by the DIC, indicating that the ISTH overt-DIC diagnostic criteria are objective. The levels of fibrin-related products are given the highest weight among abnormal laboratory test values, and 2 points are assigned for a reduction in platelet count, which lowers the specificity of DIC diagnosis in patients with leukemia.

Diagnosis of non-overt DIC (compensated DIC)

The majority of Japanese physicians initiate anticoagulant therapy when a patient has a DIC score of 5 or 6 based on the JMHLW criteria. The early treatment of DIC has been recommended, but there is only limited evidence of its efficacy. In a retrospective study³¹ that examined the effectiveness of early treatment of DIC, when treatment was given at the pre-DIC stage, at least 80% of cases showed remission of DIC, while only 8% had worsening of DIC. With a higher DIC score at the start of the treatment, the remission rate decreased, and the percentage of cases that worsened increased,

Table 4. A comparison among the JMHLW disseminated intravascular coagulation (DIC) diagnostic criteria, ISTH overt-DIC diagnostic criteria and JAAM DIC diagnostic criteria

	Overt-DIC criteria by the ISTH	DIC criteria by the JMHLW (without leukemia)	JAAM DIC diagnostic criteria
Underlying disease	0 points (essential)	1 point	0 points (essential)
Clinical symptoms	0 points	bleeding 1 point organ failure 1 point	SIRS score ≥ 3 ; 1 point
Platelet counts ($\times 10^3/\mu\text{L}$)	> 50 but < 100 ; 1 point, < 50 ; 2 points	> 80 but < 120 ; 1 point, > 50 but < 80 ; 2 points < 50 ; 3 points	> 80 but < 120 or $> 30\%$ reduction; 1 point < 80 or $> 50\%$ reduction; 3 points
Fibrin-related marker	FDP, D-dimer, SF moderate increase; 2 points, strong increase; 3 points	FDP ($\mu\text{g}/\text{mL}$) > 10 but < 20 ; 1 point, > 20 but < 40 ; 2 points, > 40 ; 3 points	FDP ($\mu\text{g}/\text{mL}$) > 10 but < 25 ; 1 point, > 25 ; 3 points
Fibrinogen (g/L)	< 1 ; 1 point	> 1 but < 1.5 ; 1 point, < 1 ; 2 points	None
PT	Prolonged PT (sec) > 3 but < 6 ; 1 point > 6 ; 2 points	PT ratio > 1.25 but < 1.67 ; 1 point, > 1.67 ; 2 points	PT ratio > 1.2 ; 1 point
Diagnosis of DIC	≤ 5 points	≥ 7 points	≥ 4 points

JAAM, Japanese Association for Acute Medicine; JMHLW, Japanese Ministry of Health, Labor and Welfare; ISTH, International Society on Thrombosis and Haemostasis; FDP, fibrin/fibrinogen degradation products; SF, soluble fibrin; PT, prothrombin

thus suggesting that DIC has a better prognosis when treatment is started an early stage.

When the period 1 week immediately before the onset of DIC is retrospectively defined as pre-DIC,³² the hemostatic molecular markers, such as the thrombin-AT complex (TAT), SF, and plasminogen activator inhibitor-I (PAI-I) showed usefulness for the diagnosis of pre-DIC. Of these markers, SF was the most useful.³³ Many investigations have been carried out in Japan for the diagnosis of pre-DIC, but no diagnostic criteria have yet been established. Table 5 provides a modified, but still preliminary, draft of diagnostic criteria for non-overt DIC.³⁴ In this draft, the sensitivity of global coagulation tests was improved by including changes in their values over time. It has also adopted measurement of vascular endothelial cell markers as AT and PC, and SF or TAT as markers of the activation of coagulation.

Comparison of the JMHLW DIC diagnostic criteria, ISTH overt-DIC diagnostic criteria, and JAAM acute phase DIC diagnostic criteria

A prospective study by the Japanese Society of Thrombosis and Hemostasis (JSTH) evaluated these three sets of criteria. Among the cases registered for the study, twice as many patients were diagnosed as having DIC using the JAAM acute phase DIC diagnostic criteria as compared to the other two sets of criteria.³⁵ Based on this finding, the acute phase DIC diagnostic criteria were the most sensitive, followed by the JMHLW criteria and the ISTH overt-DIC criteria. The percentage of patients diagnosed with late onset DIC, i.e., those who were not diagnosed to have DIC at registration, but who developed DIC within 1 week, was in the range of 12.1%

to 13.9%. All three sets of criteria gave more or less similar results (Table 6).

Since there is no gold standard for the diagnosis of DIC, the prediction of mortality was chosen as a criterion for evaluation. The JAAM diagnostic criteria provided the best sensitivity (80.0%) for mortality, but low specificity (33.2%). Because of this, the odds ratio for this set of criteria was 1.99, and was ranked second behind the ISTH overt-DIC diagnostic criteria, which have the highest odds ratio for mortality.

Clinical laboratory tests related to DIC diagnosis

Global coagulation tests generally show prolongation of the PT, reductions in the platelet count and fibrinogen, and an increase in FDP. However, there are many exceptions. In a severe inflammatory response, such as in patients with infectious diseases, the fibrinogen level and platelet count increase, contrary to the general trend. Hepatic dysfunction, such as liver cirrhosis, decreases the platelet count and fibrinogen level, and prolongs the PT. The platelet count also markedly decreased as a result of medication, radiotherapy, bone marrow suppression, or anti-platelet antibodies. Although global coagulation tests are markers that can reflect consumptive coagulopathy, they can also lead to abnormal results when there are other underlying causes. Therefore, global coagulation tests are not specific for a diagnosis of DIC.

The PT, fibrinogen, FDP, platelet count, and vascular endothelial cell damage markers, such as AT, PC, and TM, did not show any significant difference in pre-DIC and non-DIC patients, thus suggesting that global coagulation tests and vascular endothelial cell damage markers are suitable for the diagnosis of DIC, but not for the diagnosis of pre-DIC.

Table 5. Overt disseminated intravascular coagulation (DIC) and the modified diagnostic criteria for non-overt DIC to detect a DIC or Pre-DIC state

Present data	Points	Change in data*	Points	Score
> 100	0	+ 50 > % reduction	1	=
> 50 but 100 <	1	+ 50 > % reduction	1	= A
< 50	2		0	=
< 10	0	+ 5-fold increase	1	=
> 10 but < 25	1	+ 5-fold increase	1	= B
25 >	2		0	=
> 1.0	0	+ 50 > % reduction	1	=
< 1.0 but > 0.5	1	+ 50 > % reduction	1	= C
< 0.5	2		0	=
< 14.0	0	+ Prolongation : > 2.0	1	=
> 14.0 but < 17.0	1	+ Prolongation : > 2.0	1	= D
> 17.0	2		0	=
AT < 70% 1 point				= E
FMC > 10 mg/L or TAT > 10 μg/L				= F

Diagnosis of DIC and pre-DIC: A + B + C + D + E + F ≥ 5
 AT, antithrombin; FMC, fibrin monomer complex; TAT, thrombin-AT complex

Table 6. The relationship between mortality and the diagnostic criteria

	JMHW	ISTH	JAAM
DIC	166 (40.2%)	143 (34.6%)	291 (70.5%)
Without DIC	247	270	122
Late onset DIC*	30 (12.1%)	36 (13.3%)	17 (13.9%)
Mortality from DIC	35.5% (59/166)	40.6% (58/143)	31.7% (92/291)
Sensitivity for death	51.3%	50.4%	80.0%
Specificity for death	64.9	71.4%	33.2%
Odds ratio for death	1.88 (1.22 – 2.90)	2.55 (1.65 – 3.95)	1.99 (1.19 – 3.32)
	<i>P</i> < 0.005	<i>P</i> < 0.001	<i>P</i> < 0.001

JMHLW, Japanese Ministry of Health, Labor and Welfare; ISTH, International Society on Thrombosis and Haemostasis; JAAM, Japanese Association for Acute Medicine

Late onset of DIC: The patients were not diagnosed at registration but they were diagnosed to have DIC within one week.

Hemostatic molecular markers, such as TAT, plasmin-plasmin inhibitor complex (PPIC), D-dimer, and SF are better for the diagnosis of pre-DIC, because their expression levels were significantly different at the pre-DIC stage.^{32,36} For example, TAT and prothrombin fragments 1 + 2 (F1 + 2) were increased by production of thrombin, while PPIC was increased by the production of plasmin. SF was increased by fibrin formation. D-dimer was also increased as a result of fibrinolytic activity after fibrin polymerization. FVIIa increases by the release of TF into the blood, and the expression of TF on leukocytes. TAT, F1 + 2, FVIIa, SF and D-dimer are therefore markers of activation of the coagulation system. PPIC and D-dimer are markers of activation of the fibrinolytic system. Increases in these markers are useful for detecting a pre-DIC or hypercoagulable state.

In fibrinolysis-dominant DIC, there is a reduction of the platelet count and fibrinogen level, and prolongation of the PT. In addition, a reduction in PI and plasminogen, an increase in the PPIC and a shortening of the euglobulin lysis time (ELT) can also be seen. An increase in PAI-I indicates that there is an increase in the fibrinogen level and a weakening of the fibrinolytic system. An increased TM and decreased AT and PC in the blood may be used as markers for vascular endothelial cell damage. The mechanisms responsible for changes in the TM, AT and PC levels may be 1) improper TM elimination caused by renal failure, 2) reduced production of AT and PC due to hepatic dysfunction, 3) a hyper-coagulable state, coupled with consumption of AT and PC and the release of TM, or 4) the degradation of AT and PC by proteases such as elastase, etc. The most supported theory in DIC is that vascular endothelial damage itself releases TM into the blood, and that AT and PC are leaked out of blood vessels. Vascular endothelial cell damage and the associated organ dysfunction are major factors that can worsen the prognosis of DIC. The levels of vascular endothelial cell damage markers have also been shown to correlate well with the sepsis-related organ failure assessment (SOFA) score.³⁷

TF shows a marked increase in some DIC cases, while in

others, it shows only a mild increase. This difference is believed to be because TF is active on cell membranes. Measurement of TF mRNA in leukocytes, rather than measurement of soluble TF antigen in the blood has proven to be useful for diagnosis of infectious DIC.

PROGNOSIS OF DIC

Table 7 shows the mortality for severe sepsis patients treated with AT,⁵ recombinant APC,⁶ and recombinant TFPI³⁸ and for DIC treated with recombinant TM⁷ and plasma-derived APC.³⁹ The mortality of DIC patients can vary, depending on the DIC diagnostic criteria used. Among the placebo-treated patients with severe sepsis, the mortality of non-DIC patients was about 22%. This result was doubled (40-45%) in patients with associated DIC, thus suggesting that the complication with DIC worsened the outcome of sepsis. Although the bias from the physician was taken into account, that of patients treated with APC or TM was about 25-28%. In cases of infection, treatment of the DIC can probably reduce mortality by 10-15%. The mortality of DIC patients without infection was relatively low, at about 17-40%, and further investigation will be needed to determine whether the treatment of such DIC would significantly reduce the mortality.

New advances in adjuvant therapies, such as the administration of granulocyte colony-stimulating factor, blood transfusions and all-trans retinoic acid (ATRA) against APL reduce the incidence of DIC and the associated mortality. In emergency medicine, the treatment of underlying diseases has improved, but the incidence of DIC as a complication has increased. The number of diagnosed infectious DIC cases is expected to increase further following the success of clinical trials with APC on severe sepsis.⁶ However, the prognosis of sepsis associated with DIC is still poor. As DIC in critical care is still not diagnosed at an early stage, it is possible that JMHLW DIC diagnostic criteria may not be appropriate for evaluating patients with sepsis. The JMHLW DIC criteria are

Table 7. The mortality of patients with non-DIC or DIC

Treatment	Infectious disease			Non-infectious disease
	A) DIC	B) Non-DIC	C) A) + B)	DIC
Recombinant TM	28.0%			17.2%
Plasma-derived APC				20.4%
Recombinant APC	25.4%	22.1%	24.0%	
Plasma derived AT			37.5%	
Heparin	34.6%		28.0-36.6%	18.0-40.0%
Placebo	40.0-46.2%	22.2-26.5%	39.9-43.6%	

DIC, disseminated intravascular coagulation; TM, thrombomodulin; APC, activated protein C; AT, antithrombin

based on an increase in FDP and a decrease in the fibrinogen level, but in case of infectious DIC, the change in FDP and fibrinogen is small. Therefore, diagnostic criteria with a greater sensitivity need to be prepared for infectious DIC.

The JAAM^{3,40} acute phase DIC diagnostic criteria have improved sensitivity, but have not improved in specificity. When using the diagnostic criteria based on global coagulation tests, lowering of the specificity is unavoidable to obtain increased sensitivity. A better strategy to improve sensitivity, while maintaining specificity, is to use hemostatic molecular markers as are used the modified version of the non-overt DIC diagnostic criteria.³⁴ However, there has been little evidence gathered for the use of hemostatic molecular markers.

The DIC subcommittee of the JSTH SSC has plans to gather evidence from prospective studies to define cut-off values for hemostatic molecular markers. Measurement of these markers is costly and time-consuming to perform, but are highly specific for the diagnosis of DIC. It is hoped that with automation of the analysis and cost reduction, these markers will be more widely used. Different sets of DIC diagnostic criteria are used in Japan and Western countries. The evidence for the ability of these criteria to accurately diagnose DIC and predict the survival rate is still minimal. Therefore, new diagnostic criteria from prospective studies which consider the relationship between the criteria and prognosis, which can help improve patient survival, need to be established.

CONCLUSION

In order to improve the prognosis of DIC, it is important to diagnose the condition accurately and as early as possible. It is hoped that new diagnostic criteria using hemostatic molecular markers, which have both high sensitivity and specificity, will soon be established.

REFERENCES

- 1 Aoki N, Hasegawa H: [About revised version of "Auxiliary test

- findings and results for diagnostic" in diagnostic criteria for DIC: A study report by the research committee on blood coagulation on abnormalities in 1987. Special diseases designated by Japanese Ministry of Health and Welfare]. pp.37-41, 1988
- 2 Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M: Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation - On behalf of the Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). *Thromb Haemost* 86:1327-1330, 2001
- 3 Gando S, Iba T, Eguchi Y, Ohtomo Y, Okamoto K, *et al.*; Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) Study Group: A multi-center, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients : comparing current criteria. *Crit Care Med* 34:625-631, 2006
- 4 Wada H: Disseminated intravascular coagulation. *Clin Chim Acta* 344:13-21, 2004
- 5 Warren BL, Eid A, Singer P, Pillay SS, Carl P, *et al.*; the KyberSept Trial Study Group : Caring for the critically ill patient. High-dose antithrombin in severe sepsis. A randomized controlled trial. *JAMA* 286:1869-1878, 2001
- 6 Bernard GR, Vincent JL, Laterre PF, Larosa SP, Dhainaut JF, *et al.*: Efficacy and safety of recombinant human protein C for severe sepsis. *New Engl J Med* 8:699-709, 2001
- 7 Saito H, Maruyama I, Shimazaki S, Yamamoto Y, Aikawa N, *et al.*: Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation : results of a phase III, randomized, double-blind clinical trial. *J Thromb Haemost* 5:31-41, 2007
- 8 Müller-Berghaus G, ten Cate H, Levi M: Disseminated intravascular coagulation: Clinical spectrum and established as well as new diagnostic approaches. *Thromb Haemost* 82:706-712, 1999
- 9 Nakagawa M: An investigation report concerning incidence and underlying cause of DIC in Japan: A study report by the research committee on blood coagulation on abnormalities in 1998. Special diseases designated by Japanese Ministry of Health and Welfare. pp.157-164, 1999
- 10 Okamoto K, Wada H, Hatada T, Uchiyama T, Kawasaki K, *et al.*; Japanese Society of Thrombosis Hemostasis/DIC subcommit-

- tee : Frequency and hemostatic abnormalities in pre-DIC patients. *Thromb Res* 126:74-78, 2010
- 11 Wada H, Asakura H, Okamoto K, Iba T, Uchiyama T, *et al.*; Japanese Society of Thrombosis Hemostasis/DIC subcommittee: Expert consensus for the treatment of disseminated intravascular coagulation in Japan. *Thromb Res* 125:6-11, 2010
 - 12 Wada H, Nagano T, Tomeoku M, Kuto M, Karitani Y, *et al.*: Coagulant and fibrinolytic activities in the leukemic cell lysates. *Thromb Res* 30:315-322, 1983
 - 13 Taylor FB Jr, Chang A, Ruf W, Morrissey JH, Hinshaw L, *et al.*: Lethal *E. coli* septic shock is prevented by blocking tissue factor with monoclonal antibody. *Circ Shock* 33:127-134, 1991
 - 14 Creasey AA, Chang AC, Feigen L, Wun TC, Taylor FB Jr, *et al.*: Tissue factor pathway inhibitor reduces mortality from *Escherichia coli* septic shock. *J Clin Invest* 91:2850-2860, 1993
 - 15 Taylor FB, Chang AC, Peer G, Li A, Ezban M, *et al.*: Active site inhibited factor VIIa (DEGR VIIa) attenuates the coagulant and interleukin-6 and -8, but not tumor necrosis factor, responses of the baboon to LD 100 *Escherichia coli*. *Blood* 91:1609-1615, 1998
 - 16 Yamamuro M, Wada H, Kumeda K, Inoue A, Tsuji I, *et al.*: Changes in plasma tissue factor pathway inhibitor levels during the clinical course of disseminated intravascular coagulation. *Blood Coagul Fibrinolysis* 9:491-497, 1998
 - 17 Levi M: Pathogenesis and treatment of disseminated intravascular coagulation in the septic patient. *J Crit Care* 16:167-177, 2001
 - 18 Lien E, Means TK, Heine H, Yoshimura A, Kusumoto S, *et al.*: Toll-like receptor 4 imparts ligand-specific recognition of bacterial lipopolysaccharide. *J Clin Invest* 105:497-504, 2000
 - 19 Thomas JA: Toll genes and responsiveness to bacterial endotoxin. *New Engl J Med* 342:664-665, 2000
 - 20 Taylor FB, Haddad PA, Hack E, Chang AC, Peer GT, *et al.*: Two-stage response to endotoxin infusion into normal human subjects : Correlation of blood phagocyte luminescence with clinical and laboratory markers of the inflammatory, hemostatic response. *Crit Care Med* 29:326-334, 2001
 - 21 Asakura H, Suga Y, Aoshima K, Ontachi Y, Mizutani T, *et al.*: Marked difference in pathophysiology between tissue factor- and lipopolysaccharide-induced disseminated intravascular coagulation models in rats. *Crit Care Med* 30:161-164, 2002
 - 22 Weiss SJ: Tissue destruction by neutrophils. *N Engl J Med* 320:365-376, 1989
 - 23 Okajima K: Antithrombin prevents endotoxin-induced pulmonary vascular injury by inhibiting leukocyte activation. *Blood Coagul Fibrinolysis* 9 (Suppl 2):S25-S37, 1998
 - 24 Bone RC: Toward an epidemiology and natural history of SIRS (systemic inflammatory response syndrome). *JAMA* 268:3452-3455, 1992
 - 25 Gando S, Kameue T, Nanzaki S, Nakanishi Y: Disseminated intravascular coagulation is a frequent complication of systemic inflammatory response syndrome. *Thromb Haemost* 75:224-228, 1996
 - 26 Nakajima T, Kitajima I, Shin H, Takasaki I, Shigeta K, *et al.*: Involvement of NF- κ B activation in thrombin-induced human vascular smooth muscle cell proliferation. *Biochem Biophys Res Commun* 204:950-958, 1994
 - 27 Souter PJ, Thomas S, Hubbard AR, Poole S, Romisch J, *et al.*: Antithrombin inhibits lipopolysaccharide-induced tissue factor and interleukin-6 production by mononuclear cells, human umbilical vein endothelial cells, and whole blood. *Crit Care Med* 29:134-139, 2001
 - 28 Taylor FB Jr, Stearns-Kurosawa DJ, Kurosawa S, Ferrell G, Chang AC, *et al.*: The endothelial protein C receptor aids in host defense against *Escherichia coli* sepsis. *Blood* 95:1680-1686, 2000
 - 29 Kobayashi N, Maegawa T, Takada M, Tanaka H, Gonmori H: Criteria for diagnosis of DIC based on the analysis of clinical and laboratory findings in 345 DIC patients collected by the Research Committee on DIC in Japan. *Bibl Haematol* (49):265-275, 1983
 - 30 Wada H, Gabazza EC, Asakura H, Koike K, Okamoto K, *et al.*: Comparison of diagnostic criteria for disseminated intravascular coagulation (DIC): diagnostic criteria of the International Society of Thrombosis and Hemostasis and of the Japanese Ministry of Health and Welfare for overt DIC. *Am J Hematol* 74:17-22, 2003
 - 31 Wada H, Wakita Y, Nakase T, Shimura M, Hiyoyama K, *et al.*: Outcome of disseminated intravascular coagulation in relation to the score when treatment was begun. *Mie DIC Study Group. Thromb Haemost* 74:848-852, 1995
 - 32 Wada H, Minamikawa K, Wakita Y, Nakase T, Kaneko T, *et al.*: Hemostatic study before onset of disseminated intravascular coagulation. *Am J Hematol* 43:190-194, 1993
 - 33 Wada H, Wakita Y, Nakase T, Shimura M, Hiyoyama K, *et al.*: Increased plasma-soluble fibrin monomer levels in patients with disseminated intravascular coagulation. *Am J Hematol* 51:255-260, 1996
 - 34 Wada H, Hatada T, Okamoto K, Uchiyama T, Kawasaki K, *et al.*; Japanese Society of Thrombosis Hemostasis/DIC subcommittee: Modified non-overt DIC diagnostic criteria predict the early phase of overt-DIC. *Am J Hematol* 85:691-694, 2010
 - 35 Takemitsu T, Wada H, Hatada T, Ohmori Y, Ishikura K, *et al.*: Prospective evaluation of three different diagnostic criteria for disseminated intravascular coagulation. *Thromb Haemost* 105:40-44, 2011
 - 36 Wada H, Mori Y, Shimura M, Hiyoyama K, Nakasaki T, *et al.*: Poor outcome in disseminated intravascular coagulation or thrombotic thrombocytopenic purpura patients with severe vascular endothelial cell injuries. *Am J Hematol* 58:189-194, 1998
 - 37 Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, *et al.*: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine (see contributors to the project in the appendix). *Intensive Care Med* 22:707-710, 1996
 - 38 Abraham E, Reinhart K, Opal S, Demeyer I, Doig C, *et al.*; OPTIMIST Trial Study Group : Efficacy and safety of tifacogin

Kaneko T & Wada H

(recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. *JAMA* 290:238-247, 2003

39 Aoki N, Matsuda T, Saito H, Takatsuki K, Okajima K, *et al.*: A comparative double-blind randomized trial of activated protein C and unfractionated heparin in the treatment of disseminated intravascular coagulation. *Int J Hematol* 75:540-547, 2002

40 Gando S, Saitoh D, Ogura H, Mayumi T, Koseki K, *et al.*;

Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) Study Group: Natural history of disseminated intravascular coagulation diagnosed based on the newly established diagnostic criteria for critically ill patients: results of a multicenter, prospective survey. *Crit Care Med* 36:145-150, 2008