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Evaluation of the International Society on Thrombosis & Haemostasis scoring system & its modifications in diagnosis of disseminated intravascular coagulation: A pilot study from southern India

Pooja Sai Muddana[†], Sitanshu Sekhar Kar[2] & Rakhee Kar[1]

Departments of [1]Pathology & [2]Preventive and Social Medicine, [†]Jawaharlal Institute of Postgraduate Medical Education & Research, Puducherry, India

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***Background & objectives*: Diagnosis of disseminated intravascular coagulation (DIC) rests primarily on the clinical profile along with supportive laboratory tests. The International Society on Thrombosis and Haemostasis (ISTH) had proposed a scoring system for the diagnosis of overt DIC. However, fibrinogen values which are supposed to be low are often found to be elevated due to the associated inflammation seen in some cases. Moreover, peripheral smear is known to show schistocytes, which is also not included in the score. This study was done to evaluate ISTH scoring system and its modifications in suspected DIC.**

***Methods*: Fifty-six patients were enrolled for the present study of whom; in four, fibrinogen assay could not be done. Modifications in the ISTH scoring with the exclusion of fibrinogen, *i.e.* modified ISTH (MI) score and subsequent inclusion of schistocytes, *i.e.* modified ISTH with schistocytes (MIS) score, were used. The modified scores were analyzed for diagnostic accuracy parameters and agreement with ISTH score.**

***Results*: Amongst 56 cases, 9/52 (17.3%), 22 (39.3%) and 17 (30.4%) were diagnosed as positive for overt DIC by ISTH, MI and MIS scores and mortality was 33, 22.7 and 17.6 per cent, respectively. The sensitivity, specificity, positive and negative predictive values for the MI score were 100, 74.4, 45 and 100 per cent and for MIS score were 100, 86, 60 and 100 per cent, respectively. The agreement between MI score and MIS score with ISTH score was moderate [κ=0.502, 95% confidence interval (CI): 0.272-0.732, *P*<0.001] and substantial (κ=0.681, 95% CI: 0.45-0.91, *P*<0.001).**

***Interpretation & conclusions*: In the present study, the calculated mortality was highest by ISTH score. Best agreement was between MIS score and ISTH score. In a resource-constrained setup where fibrinogen assay and therefore ISTH score is difficult, it is suggested that MIS score can be considered.**

Key words Disseminated intravascular coagulation - disseminated intravascular coagulation scoring - fibrinogen - ISTH score - modified ISTH score - mortality - overt DIC - schistocytes

Disseminated intravascular coagulation (DIC) may present either as latent with compensated activation of coagulation or as overt depending on the underlying disease, intensity of coagulation activation

and deficiency of the natural anticoagulant pathways[1]. Since there is no gold standard diagnostic test for DIC; the diagnosis is based purely on clinical suspicion related to the underlying disorder and the abnormalities of blood coagulation tests incorporated into diagnostic scoring systems[1]. The International Society on Thrombosis and Haemostasis (ISTH) hence proposed a scoring system for overt DIC[2,3], with a sensitivity and specificity of 91 and 97 per cent, respectively[4]. This includes the parameters such as platelet count (PC), increase in fibrin degradation product (FDP)/D-dimers, prolongation of prothrombin time (PT) and fibrinogen level. Apart from the ISTH scoring system, various other scoring systems have been proposed and used in different centres; many of these are based on certain common parameters with some modifications[5].

In our centre, for cases of suspected DIC, in addition to the above tests, peripheral blood smear (PBS) to detect schistocytes is also done routinely. Some modifications in the ISTH scoring were tried such as exclusion of fibrinogen from the score, *i.e.* modified ISTH (MI) score, and subsequent inclusion of schistocytes, *i.e.* modified ISTH with schistocytes (MIS) score. This was due to the fact that fibrinogen being often elevated due to the usually associated inflammation is not a sensitive marker for DIC[6] and has a non-linear association with elevated DIC scores[7] and the presence of schistocytes[8] is frequently encountered in DIC. The present study aimed to evaluate the ISTH scoring system and its modifications for the diagnosis of DIC and also analyze the level of agreement between them.

Material & Methods

Study design and participant inclusion/exclusion criteria: This was a cross-sectional pilot study conducted over a two-month period in a tertiary care health facility, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, in southern India. Patients suspected to have DIC and whose haematology workup was available (n=56) were included by convenient sampling method. Patients diagnosed with other known causes of thrombocytopaenia, with inherited bleeding disorders and on anticoagulant therapy and paediatric cases were excluded. The study was approved by the Institutional Ethics Committee. Informed consent was obtained, and data confidentiality was maintained.

Testing of suspected disseminated intravascular coagulation (DIC) cases: The following investigations were done for the confirmation of suspected DIC: PC (XT 2000i, Sysmex Corporation, Kobe, Japan), PBS (Leishman's stain), FDP (paracoagulation test using protamine sulphate), D-dimer (latex agglutination test) and PT and fibrinogen assay (STA compact CT, Diagnostica Stago, Asnières-sur-Seine, France). The values of individual parameters for the calculation of ISTH DIC score and its proposed modifications are mentioned in Table I. ISTH score was calculated for 52 cases as fibrinogen assay had not been done for four; however, MI and MIS scores were calculated for all 56 cases.

Schistocytes were noted as present and absent; quantitation was not done. At the time of this study, the quantification of FDP/D-dimer could not be done in our laboratory. Hence, this parameter was scored in a two-tier system as score of 2 for positive and 0 for negative with the assumption that any detectable FDP/D-dimer would be having at least a moderate increase in titre. Hence, the total effective scores (denominators) were 7 for the ISTH DIC score and MIS score and 6 for MI score. A possibility of underdiagnosis of a few cases exists, but no effect on the interscore comparability was expected as the same system was followed for all the scores. The patient outcome regarding mortality was assessed during two months of patient enrolment.

Statistical analysis: Statistical analysis was carried out by SPSS software - version 20.0. (Statistical Package for Social Sciences (SPSS) for windows Version 20.0. IBM Corp., Armonk, NY, USA). The agreement between MI and MIS scores with ISTH score was done by kappa analysis. The kappa value was interpreted as follows: ≤0 indicating no agreement, 0.01-0.20 as slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial and 0.81-1.00 as almost perfect agreement[9]. Diagnostic accuracy assessed as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the diagnosis by two modified scoring systems was calculated by considering the diagnosis by ISTH scoring system as the gold standard. The difference in mortality amongst cases diagnosed positive by various scores was compared by Fisher's exact test. All statistical analysis was carried out at five per cent level of significance, and $P<0.05$ was considered statistically significant.

Results & Discussion

A total of 56 suspected DIC cases comprising 23 (41.1%) males and 33 (58.9%) females with a mean

Table I. Components of International Society on Thrombosis and Haemostasis (ISTH) disseminated intravascular coagulation (DIC) scoring, modified ISTH score and modified ISTH with schistocytes score

Parameter	ISTH DIC score	MI score	MIS score
PC ($\times 10^9$/l)	≥100=0	≥100=0	≥100=0
	50-<100=1	50-<100=1	50-<100=1
	<50=2	<50=2	<50=2
FDP/D-dimer	No increase=0	No increase=0	No increase=0
	Moderately increased=2	Moderately increased=2	Moderately increased=2
	Strongly increased=3	Strongly increased=3	Strongly increased=3
Prolongation of PT (s)	<3=0	<3=0	<3=0
	≥3-<6=1	≥3-<6=1	≥3-<6=1
	≥6=2	≥6=2	≥6=2
Fibrinogen level (g/l)	≥1=0	Not included	Not included
	<1=1		
Schistocytes	Not included	Not included	Absent=0
			Present=1
Diagnostic score for overt DIC	≥5/8	≥4/7	≥5/8
Considered diagnostic score (in this study) for overt DIC	≥5/7	≥4/6	≥5/7
	FDP/D-dimer quantification was not done (considered values for FDP/D-dimer: Negative=0, positive=2)		

PC, platelet count; FDP, fibrin degradation product; PT; prothrombin time; MI, modified ISTH; MIS, modified ISTH with schistocytes

age of 39.3 yr (standard deviation=14.65, range: 18-76) were included. The underlying presenting conditions were snake bite (17, 30.4%), obstetric complications (12, 21.4%), haematological malignancies (4, 7.1%), sepsis (11, 19.6%), trauma (3, 5.4%) and other miscellaneous conditions (9, 16.1%).

ISTH scoring was done for 52 cases, of which nine (17.3%) were positive for overt DIC. According to the MI and MIS scores, 22 (39.3%) and 17 (30.4%) were diagnosed positive for overt DIC, respectively. All the nine cases diagnosed as positive by ISTH score were found to be positive according to the other scores as well; however, a lot of cases had elevated fibrinogen levels which limited their diagnosis. It was observed that amongst the 11 cases with a score of 4 that were reported as negative for overt DIC according to the ISTH scoring, all were positive by MI scoring and six were positive by MIS scoring. Fibrinogen level has previously been reported to have less sensitivity[6], shown to lack a significant correlation with DIC score and other biomarkers of sepsis[10]. Furthermore, it has also been hypothesized that its exclusion does not affect the accuracy of the scoring system[4].

The frequencies of derangement of various parameters used for scoring and mortality amongst all cases and those diagnosed positive by various scores are given in Table II. Thrombocytopaenia, PT prolongation and derangement in fibrin-related parameters in DIC-positive cases were comparable across the three scoring systems. The proportion of DIC-positive cases showing the presence of schistocytes according to the ISTH, MI and MIS scores was 77.77 (7/9), 68.18 (15/22) and 88.23 (15/17) per cent, respectively.

The overall mortality was 21 per cent (12/56); nine patients having died due to sepsis and related complications, one due to obstetric complications and two due to other miscellaneous causes. The percentage of mortality among the positively diagnosed DIC cases according to the ISTH, MI and MIS scores was 33 (3/9), 22.72 (5/22) and 17.64 (3/17) per cent, respectively, and was not significant. Multiple studies have shown that ISTH score was effective in predicting mortality and severity of the disease condition[4,11]. Low fibrinogen levels of ≤1 g/l and 1-1.5 g/l have been shown to be independently associated with 28 day mortality compared to fibrinogen level above 1.5 g/l[5]. In this study, the overall mortality and mortality in overt DIC-positive cases by proposed modifications of ISTH score were lower compared to that by ISTH score. Hence, there is a likelihood of overdiagnosis of

Table II. Frequencies of derangement of individual parameters and mortality amongst all enrolled cases (n=56) and cases diagnosed positive for overt DIC by modified ISTH scoring (n=22), modified ISTH with schistocytes score (n=17) and ISTH score (n=9)

Parameter	All clinically suspected cases (%)	Positive for overt DIC by various scoring systems		
		MI score (%)	MIS score (%)	ISTH DIC score (%)
Number of cases (n)	56	22	17	9 (out of 52 cases)
Thrombocytopaenia (<100×10^9/l)	47 (83.92)	20 (90.90)	16 (94.11)	9 (100)
PT prolongation (≥ three seconds)	26 (46.42)	19 (86.36)	14 (82.35)	9 (100)
Fibrinogen (<1 g/l) (not done in four cases)	2 (3.85)	2 (10)	2 (13.33)	2 (22.22)
FDP/D-dimer (positive)	26 (46.42)	16 (72.72)	14 (82.35)	7 (77.77)
Schistocytes (present)	39 (69.64)	15 (68.18)	15 (88.23)	7 (77.77)
Mortality	12/56 (21)	5/22 (22.72)	3/17 (17.64)	3/9 (33)

Table III. Cross-tabulation of data (n=52) and diagnostic accuracy parameters of modified ISTH score and modified ISTH with schistocytes score considering ISTH disseminated intravascular coagulation score as gold standard

Parameters	ISTH DIC score		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Positive (9)	Negative (43)				
MI score						
Positive	9	11	100	74.4	45	100
Negative	0	32				
MIS score						
Positive	9	6	100	86	60	100
Negative	0	37				

PPV, positive predictive value; NPV, negative predictive value

overt DIC by the proposed modifications compared to ISTH score.

The agreement between MI score and MIS score with ISTH score was moderate (κ=0.502, P<0.001) [95% confidence interval (CI): 0.272-0.732] and substantial (κ=0.681, P<0.001) (95% CI: 0.45-0.91), respectively. The cross-tabulation of data for cases where all three scoring systems were used (n=52) and the diagnostic accuracy parameters of the modifications of scoring system are mentioned in Table III. The sensitivity, specificity, PPV and NPV for diagnosis of overt DIC by MI score were 100, 74.4, 45 and 100 per cent and for MIS score were 100, 86, 60 and 100 per cent, respectively.

A scoring system brings objectivity to diagnosis and reduces overdiagnosis. In a resource-constraint setup where quantification of FDP/D-dimer and fibrinogen assay might be difficult to perform, proposed modifications of ISTH scoring for the diagnosis of DIC can be tried. Since the best agreement was observed between MIS and ISTH scores. MIS scoring was 100 per cent sensitive and 86 per cent specific compared to the ISTH scoring though the mortality in cases positive for overt DIC by MIS scoring (17.64%) were less compared to that by ISTH scoring (33%). Several DIC scoring systems have been proposed to make a diagnosis of overt DIC[1]. The present study comprehensively analyzed the haematological derangements which are components of the ISTH scoring system and also devised slight modifications of the existing ISTH scoring system to make it adaptable to resource-constraint settings. However, the limitations of this study were the small sample size (n=56), non-availability of fibrinogen assay for four cases reducing the number of cases where ISTH scoring could have been done (n=52) and a lack of quantitative D-dimer/FDP values. Moreover, no repeat scoring was done for any of the patients, thereby limiting the information to one snapshot in the entire pathological process.

In conclusion, MIS scoring is a feasible alternative to ISTH scoring in the diagnosis of overt DIC. Overall,

larger population studies are necessary to establish the utility of the proposed modifications in this study.

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***Conflicts of Interest*:** None.

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For correspondence: Dr Rakhee Kar, Department of Pathology, Jawaharlal Institute of Postgraduate Medical Education & Research, Puducherry 605 006, India
e-mail: drrakheekar@gmail.com