DOI: 10.7860/NJLM/2023/64517.2758

Original Article

Pathology Section

Diagnosis of Disseminated Intravascular Coagulation in Patients Suffering from Sepsis using the Modified International Society of Thrombosis and Haemostasis Criteria and Japanese Association of Acute Medicine Criteria

DEEPTI RAVI VOBBILISETTY[1], SHUBHAJYOTI N PORE[2], ANIL R JOSHI[3]

ABSTRACT

Introduction: The international task force defines sepsis as 'life-threatening organ dysfunction caused by a dysregulated host response to infection'. Disseminated Intravascular Coagulation (DIC) is a coagulopathy syndrome that causes microvascular and macrovascular thrombosis and increases the risk of bleeding due to consumptive coagulopathy. Sepsis causes dysfunction in coagulation due to release of inflammatory markers which leads to inappropriate deposition of intravascular fibrin. In order to facilitate the diagnostic process for detecting DIC, the scoring system recommended by International Society of Thrombosis and Haemostasis (ISTH) and Japanese Association of Acute Medicine (JAAM) were used which are based on the global coagulation tests such as the platelet count, Prothrombin time, International Normalised Ratio (INR) and Fibrin Degradation Products (FDPs)/D-dimer.

Aim: To determine the prevalence and outcome of DIC in patients suffering from sepsis using ISTH criteria and JAAM criteria.

Materials and Methods: A prospective cohort study was carried out from January 2021 to July 2022 in the Haematology Section of Pathology Department of Government Medical College and Hospital, Aurangabad, Maharashtra, India. Hundred patients suffering from clinically suspected sepsis were included in the study. Venous blood was collected from patients in Ethylene Diamine Tetra-acetic Acid (EDTA) and Citrate bulbs. The tests performed were Complete Blood Count (CBC), Prothrombin Time (PT), International Normalised Ratio (INR) and D-Dimer. CBC was performed on Fully-automated three part cell counter. PT, INR, D-Dimer testing was done on fully-automated coagulometer. The above test results were used to diagnose DIC in patients suffering from sepsis using the modified ISTH and JAAM criterias. The results were analysed using Microsoft excel 2019 i.e., Chi-square test was applied for p-value calculation.

Results: Out of 100 patients with clinically suspected sepsis 35 patients (35%) suffered from Overt DIC using ISTH criteria and 58 patients (58%) suffered from DIC using JAAM criteria. The total mortality in patients with sepsis in the present study was 40%. The mortality in patients with DIC in sepsis using the ISTH criteria was 26 patients (74.28%) and 37 patients (63.79%) using the JAAM criteria.

Conclusion: Coagulation abnormalities are widely prevalent in patients with sepsis and are likely to play a key role in multi-organ dysfunction. Both ISTH and JAAM criteria are good predictors of mortality.

Keywords: Coagulopathy, Comparison, Microvascular thrombosis, Prevalence

INTRODUCTION

The international task force defines sepsis as 'life-threatening organ dysfunction caused by a dysregulated host response to infection' [1]. DIC is a coagulopathy syndrome that causes microvascular and macrovascular thrombosis and increases the risk of bleeding due to consumptive coagulopathy [2]. Consumption of clotting factors due to ongoing thrombosis eventually leads to a hypocoagulable state [2]. There is concurrent activation of the coagulation cascade and fibrinolytic system; however, as the syndrome progresses, through consumption of the prothrombotic and antithrombotic factors and the profibrinolytic and antifibrinolytic factors, the syndrome transforms into a haemorrhagic or thrombotic state [3-6].

Various underlying clinical conditions can have an effect on the laboratory parameters that are usually obtained to diagnose DIC, such as Global coagulation tests which include the platelet count, Prothrombin Time (PT), Fibrinogen, and Fibrin Degradation Products (FDPs). In order to facilitate the diagnostic process for detecting DIC, the use of a scoring system is recommended by four different guidelines. Two diagnostic criteria incorporating similar global coagulation tests have been established by the modified ISTH and JAAM [7-10]. Each of them has their own advantages and drawbacks. A significant difference is that the former criteria cover all the causes of DIC, whereas the latter were specially designed for the diagnosis of acute DIC [11]. The ISTH overt DIC score is useful and specific for diagnosing DIC due to infective and non infectious etiologies [12,13]. The JAAM score is sensitive for detecting septic DIC [9,13]. Very few studies have been carried out regarding the diagnosis and prevalence of DIC in patients suffering from sepsis in India [14-16]. The major studies that have been published are from Japan. [8,9,11,13,17,18] and other places outside India [19-21]. Hence, aim of the present study was the diagnosis, prevalence and outcome of DIC in patients suffering from sepsis using ISTH criteria and JAAM criteria and their comparison.

MATERIALS AND METHODS

A prospective cohort study of DIC in patients suffering from clinically suspected sepsis was conducted in the Department of Pathology, Government Medical College and Hospital, Aurangabad, Maharashtra, India, from January 2021 to July 2022. The study was done after due permission from the Institutional Ethics Committee and Review Board and after taking written informed consent from the patients with ethical number as IEC no. Pharma/IEC-GMCA/20/2020.

Inclusion criteria: Patients suffering from clinically suspected sepsis were included in the study.

The Systemic Inflammatory Response Syndrome (SIRS) is define by the presence of two or more of the criteria listed below [7]:

1.Temperature >100.4ºF or <36ºC

2.Heart Rate >90 beats per minute.

3.Respiratory Rate >20 per minute

4.Total leucocyte count >12000 or <4000/cumm

Exclusion criteria: Non co-operative patients/patients who do not give consent, those patients other than acute DIC with deranged coagulation profile and those suffering from congenital coagulation disorders were excluded from the study.

Study Procedure

The parameters studied were CBC for the platelet counts, coagulation tests i.e., PT, INR, D-Dimer. A 2 mL blood sample was collected in EDTA and citrate bulbs, respectively.

Platelet count: Samples were run on fully-automated three part cell counter H-360 ERBA for platelet counts which works on the principle of electrical impedance.

Coagulation assay: The tests done on plasma: PT, D-Dimer, were performed on sta-satellite max fully-automated coagulometer, which works on the principle of chronometric analysis and photometric analysis: colorimetry or immunology.

Modified ISTH Criteria diagnosis of DIC in sepsis [14] and JAAM criteria for the diagnosis of DIC in sepsis [9] are mentioned in [Table/Fig-1,2].

Criteria	Scoring
Platelet count (10^9/L)	
<50	2
<100	1
≥100	0
D-Dimer levels (µg/mL)	
>4	3
>0.39	2
≤0.39	0
Prothrombin Time (PT) (sec)	
>20.5	2
>17.5	1
≤17.5	0
Overt DIC status requires total score	≥5
Non overt DIC status requires total score	3-4

[Table/Fig-1]: Modified ISTH criteria for the diagnosis of DIC in sepsis [14].

Criteria	Scoring
Platelet count (10^9/L)	
<80	3
≥80 AND <120	1
SIRS criteria	
≥3	1
D-Dimer levels (mg/L)	
≥25	3
≥10 and <25	1
International Normalised Ratio (INR)	
≥1.2	1
DIC status requires total score	>=4

[Table/Fig-2]: JAAM criteria for the diagnosis of DIC in sepsis [9].

STATISTICAL ANALYSIS

Data entered systematically in Microsoft (MS) excel 2019 and represented in tabular format and graphical format as applicable. Frequency and percentage was calculated wherever necessary. Appropriate tests of significance i.e., Chi-square test for p-value was derived using excel functions and Statistical Package for Social Sciences (SPSS) 20.0.

RESULTS

During the study period, samples of 100 patients in sepsis were sent to the Department. The mean age of the patients included in the study was 52.3±17.5 years, 75% of which were male. Out of the 100 patients with sepsis, 40% did not survive. The total percentage of patients with sepsis suffering from overt DIC using modified ISTH criteria is 35%, non overt DIC using modified ISTH criteria is 27% and DIC using JAAM criteria is 58%. The maximum number of patients suffering from overt DIC were in 51-80 years (18 patients) age group, 31-60 years (19 patients) in non overt DIC and 51-80 years (31 patients) of age in DIC using JAAM criteria [Table/Fig-3,4].

Variables	Overt DIC using modified ISTH criteria (35)	Non overt DIC using modified ISTH criteria (27)	No DIC (38)	p-value Overt DIC using modified ISTH criteria
	Mean±SD	Mean±SD	Mean±SD	
Age (years)	55.11±18.8	51.07±14.08	50.73±18.6	0.53
Sex (m:f)	26:9	20:7	29:9	
Temperature (degree F)	101.32±0.62	101.05±0.76	101.04±0.74	0.97
Pulse (beats/min)	112.6±17.57	101.74±23.47	98.8±13.6	0.16
Respiration rate (/min)	22.57±3.28	22.07±4.96	20.15±3.99	0.58
Haemoglobin (Hb) (g/dL)	10.07±2.31	9.86±2.46	11.68±2.8	0.63
Total Leucocyte Count (TLC) (cumm)	19423±9145	18700±8568	14884±5655	**<0.001**
Platelet count (x10^3/uL)	75.88±50.18	168.81±102.58	208.21±76.72	**<0.001**
Prothrombin Time (PT) (secs)	25.57±7.2	19.81±7.15	14.92±3.18	**0.005**
INR	1.89±0.54	1.46±0.55	1.09±0.23	0.44
D-dimer (µg/mL)	9.48±4.29	6.67±4.05	1.2±0.82	**<0.001**
DIC Score	5.65±0.8	3.51±0.5	1.05±0.98	**<0.001**
Death (number)	26	9	5	<0.001

[Table/Fig-3]: Different relevant clinical features of patients suffering from sepsis with Disseminated Intravascular Coagulation (DIC) using the modified ISTH criteria. Bold p-values are significant; INR: International normalised ratio

Variables	JAAM positive (58)	JAAM negative (42)	p-value JAAM criteria
	Mean±SD	Mean±SD	
Age (years)	54.2±17.69	49.8±17.17	0.53
Sex (M:F)	44:14	31:11	
Temperature (degree F)	101.29±0.67	100.95±0.69	0.97
Pulse (beats/min)	109.7±20.63	97.09±13.34	0.20

Respiration rate (/min)	22.7±3.78	19.88±4.09	0.52
Hb (g/dL)	10.12±2.43	11.32±2.82	0.72
TLC (cumm)	18843±8846	15652±6353	<0.001
Platelet count (x10^3/uL)	100.51±72.64	221.33±78.25	**<0.001**
PT (secs)	23.09±7.81	15.66±4.16	0.06
INR	1.7±0.59	1.15±0.31	0.60
D-dimer (ug/mL)	8.19±4.55	1.95±2.18	**<0.001**
SIRS score	3.13±0.94	2.21±1.11	0.53
DIC score	6.24±1.49	1.35±1.18	**<0.001**
Death (number)	37	3	**<0.001**

[Table/Fig-4]: Different relevant clinical features of patients suffering from sepsis with Disseminated Intravascular Coagulation (DIC) using JAAM criteria.
Bold p-values are significant; SIRS: Systemic inflammatory response syndrome

The percentage of males suffering from overt DIC using modified ISTH criteria with sepsis is 26% and percentage of females is 9%. The M:F ratio of patients suffering from overt DIC and non overt DIC is 2.8:1. The percentage of males suffering from DIC using JAAM criteria with sepsis is 44% and percentage of females is 14%. The M:F ratio of patients suffering from DIC using JAAM criteria is 3.14:1.

The mean age of patients suffering from DIC using the modified ISTH criteria is 55.11±18.8 years and DIC using JAAM criteria is 54.2±17.69 years. The percentage of patients in sepsis suffering from overt DIC using the modified ISTH criteria who died were 74.28%, non overt DIC using the modified ISTH criteria were 33.33% and DIC using the JAAM criteria who died were 63.79%.

DISCUSSION

The present study was done to diagnose DIC using the modified ISTH criteria and JAAM criteria in patients with sepsis, the prevalence and outcome of DIC in sepsis. The authors also compared the modified ISTH and JAAM criteria for DIC in sepsis.

The percentage of males included in the present study were 75%, similar to study by Voves C et al., 82.5% and RK Singh et al., 66.6% [15,16]. The prevalence of DIC in sepsis in the present study showed that 35% patients suffered from DIC in sepsis using the modified ISTH criteria, which was similar to the prevalence in the study by Singh RK et al., (36.5%), Takemitsu T et al., (34.6%) [16,17]. 58% patients in the present study suffered from DIC in sepsis using the JAAM criteria, which was similar to the prevalence in the study by Saito S et al., (61%) [18]. The mean age of patients with sepsis suffering from DIC in the study by Rinaldi I et al., was 49.76±13.97 years and in the present study it is 55.11±18.8 years [19].

A patient is said to be suffering from sepsis clinically when the SIRS score is more than or equal to 2. The mean heart rate of patients with sepsis suffering from DIC in the study by Kim YM et al., was 116.4±31.7 beats per minute and in the present study it was 112.6±17.57 beats per minute [20]. The heart rate was >90 beats per minute (SIRS score) in patients with sepsis. The increase in heart rate can be attributed to the toxins released by the bacteria and inflammatory mediators which are released by the body as a response to the bacteria. The mean respiratory rate of patients with sepsis suffering from DIC in the study by Ko B-S et al., was 22±4 per minute, Mauri T et al., was 22±4 per minute and in the present study it was 22±3 per minute [21,22]. The respiratory rate is >20 per minute (SIRS score) in patients with sepsis. This increase in respiratory rate can be due to the stimulation of the medullary ventilatory center by endotoxins, to compensate for increased carbon dioxide concentration and also to compensate for metabolic acidosis i.e., increased lactic acid due to tissue hypoxia [23].

The mean total leucocyte count of patients with sepsis suffering from DIC in the study by Rinaldi I et al., was 16870/cumm and in the present study, it was 19423±9145/cumm [19]. The total leucocyte count shows either leukocytosis, leucopaenia or >10% band forms/left shift (SIRS score) in patients with sepsis. In sepsis, the total leucocyte count can be normal with a shift to left i.e., immature forms of leucocytes are seen in the peripheral blood. The increase in total leucocyte count is due to body's response to inflammatory mediators.

The mean platelet count of patients with sepsis suffering from DIC in the present study is 75880±50000/uL which was similar to the study by Rinaldi I et al., with a mean platelet count of 75500/uL [19]. The normal platelet count is 1,50,000-4,50,000/uL. In DIC, due to excessive thrombin activation the platelet counts decrease due to consumption of the platelets in clot formation [23]. The reduction in platelet count is statistically significant in the study (p<0.001) in DIC vs non DIC patients with sepsis. In sepsis induced DIC, there is procoagulant upregulation, anticoagulant impairment and endothelial damage due to inflammatory markers {cytokines, Tumour Necrosis Factor (TNF), Interleukin (IL)-1, IL-6}, due to which there is diffuse thrombosis and bleeding in the patients [2].

The mean PT i.e., PT in patients with sepsis suffering from DIC in the study by Dhainaut JF et al., was 22.8 seconds and in the present study it was 25.57±7.2 seconds whereas the study Rinaldi I et al., has a mean PT of 14.85 seconds which is within the normal range [14,19]. This variation in PT can be attributed to the time at which the testing was done. The PT is a measure of tissue factor-pathway molecules. DIC is a consumptive coagulopathy, in which the PT may be normal in 50% patients and increased in 50% patients [3]. In the present study, the increase in PT is statistically significant (p=0.005).

The mean D-Dimer in patients with sepsis suffering from DIC in the present study it was 9.48 ug/mL which is similar to a study by Rinaldi I et al., with a mean D-Dimer value of 8.53 ug/mL [16]. D-Dimers are a specific type of FDP consisting of polymerised fibrin monomers that have been cross-linked by activated factor XIII and subsequently cleaved by plasmin. D-Dimers are created after intravascular coagulation and clot formation. The absence of D-Dimers is useful as a negative predictive tool to exclude the diagnosis of DIC [7]. The mean D-dimer value of this study is statistically significant (p <0.001) in patients with DIC vs non DIC in sepsis. The SIRS score in patients with sepsis in the study by Gando S et al., was 3.3±0.8, Saito S et al., was 3.5±0.5 and in the present study it was 3.13±0.94 which is comparable to both the studies [9,18]. The mean overt DIC score using the modified ISTH criteria in the study by Kim YM et al., was 5.7±0.7 and Saito S et al., was 5.5±0.5 and in the present study it was 5.65±0.8 which is similar to both the studies mentioned above [18,20]. The mean DIC score using the JAAM criteria in the study by, Singh RK et al., was 6.12±1.58 Saito S et al., was 6±1 and in the present study, it is 6.24±1.49 [16,18].

The authors found remarkable difference in prevalence between the two criteria (35% by modified ISTH vs 58% by JAAM) for diagnosing DIC in patients suffering from sepsis. Several previous studies have also compared modified ISTH and JAAM criteria. For example, the study by Singh RK et al., showed 36.5% positive cases by modified ISTH criteria and 80.4% by JAAM criteria, Takemitsu T et al., showed 34.6% positive cases by modified ISTH criteria and 70.5% by JAAM criteria and Saito S et al., showed 29% positive cases by modified ISTH criteria and 61% by JAAM criteria [16-18]. Therefore, all these studies, including the present study, found a significant increase in the incidence rate of DIC diagnosis with the JAAM criteria. The mortality in patients with sepsis suffering from DIC using the modified ISTH criteria in the present study was 74.28% which was comparable to the study by Rinaldi I et al., whose mortality rate was 76% [19]. The mortality in patients with sepsis suffering from DIC using the JAAM criteria in the present study it was 63.79% which was comparable to the study by Singh RK et al., which had a mortality rate of 64.3% [16]. The mortality rate is high using both modified ISTH and JAAM criteria which is why either of the criteria can be used for the Diagnosis of DIC in sepsis. The percentage of patients who died with overt DIC vs non DIC using the modified ISTH criteria are more than those with DIC vs non DIC using the JAAM criteria.

Limitation(s)

The total sample size of the population was small because of Coronavirus Disease-2019 (COVID-19) pandemic. The cases included were not suffering from COVID-19. As the coagulopathy induced by COVID-19 would interfere with the diagnosis of DIC in sepsis and give false results.

CONCLUSION(S)

Sepsis is a dynamic and often life-threatning host response to infection. In sepsis, the inflammation diffusely activates the coagulation system, consuming multiple clotting factors and resulting in DIC. In the present study, it was found that patients in sepsis diagnosed with DIC by either of the two criteria showed a higher severity and in hospital mortality than patients without DIC. Both modified ISTH and JAAM criteria are good predictors of mortality even though the prevalence rates of both the tests vary, which is why either can be used to identify high risk patients, this will help in early intervention and can help in the reduction of mortality.

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PARTICULARS OF CONTRIBUTORS:

1. Junior Resident, Department of Pathology, Government Medical College and Hospital, Aurangabad, Maharashtra, India.
2. Assistant Professor, Department of Pathology, Government Medical College and Hospital, Aurangabad, Maharashtra, India.
3. Professor and Head, Department of Pathology, Government Medical College and Hospital, Aurangabad, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Deepti Ravi Vobbilisetty,
A-202, Princeton, Hiranandani Estate, Patlipada, Ghodbunder Road,
Thane (w)-400607, Maharashtra, India.
E-mail: deepti15395@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Apr 10, 2023
- Manual Googling: Jun 15, 2023
- iThenticate Software: Jun 19, 2023 (13%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Apr 06, 2023**
Date of Peer Review: **Apr 27, 2023**
Date of Acceptance: **Jun 20, 2023**
Date of Publishing: **Oct 01, 2023**