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Feasibility of Applying Novel FDP Threshold Criteria to DIC Diagnostic Scoring Systems in Japanese Women with Placental Abruption

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Abstract: *Objective*: The diagnosis of disseminated intravascular coagulation (DIC) in obstetrics characterized by marked elevation of fibrin/fibrinogen degradation products (FDP) requires specific FDP criteria, however, no reference values are currently available. We previously reported the FDP criteria reflecting the degree of coagulation activity, determined by the quantitative relation between the distributions of FDP and fibrinogen. We aimed to evaluate the feasibility of applying the novel FDP criteria to four existing DIC diagnostic scoring systems, in a retrospective study of Japanese women with placental abruption. *Materials and Methods*: The study population was 68 pregnant women who had been diagnosed with placental abruption at Okayama Medical Center (Japan) between January 2008 and December 2020. DIC was clinically determined using the following four categories: plasma fibrinogen level < 100 mg/dl, hemorrhage amount at delivery ≥ 2000 g, blood product (red blood cells and fresh frozen plasma) transfusion, and renal dysfunction. Based on our previous report on the artificial intelligence analysis of the FDP distribution function, FDP criteria for the normal upper limit, moderate increase, and marked increase were defined as 20, 32, and 80 μg/ml, respectively. We applied the FDP criteria to compare four current and revised DIC diagnostic scoring systems: Japanese Ministry of Health and Welfare (JMHW), Japanese Association for Acute Medicine (JAAM), International Society on Thrombosis and Haemostasis (ISTH), and pregnancy-modified ISTH (PM-ISTH) DIC score. We used the Kruskal-Wallis test, Wilcoxon rank-sum test, and proportion test for statistical analysis. *Results*: Clinical DIC was observed in nine cases. Sensitivity was 1.00 in all DIC scoring systems. The current/revised sensitivity of the JMHW, JAAM, ISTH, and PM-ISTH systems was 1.00/1.00, 1.00/1.00, not available (NA)/1.00, and 1.00/NA, respectively. The current/revised specificity of the JMHW, JAAM, ISTH, and PM-ISTH systems was 0.864/0.864, 0.678/0.797, NA/0.864, and 0.424/NA, respectively. The specificity of the revised JMHW and revised ISTH systems was higher than for the current JAAM ($P < 0.05$) and current PM-ISTH ($P < 0.0001$) systems. The specificity of the revised JAAM improved from 0.678 to 0.797. *Conclusion*: Our novel proposed FDP criteria are potentially useful for diagnosis of DIC in placental abruption.

Keywords: Diagnostic Tests, Disseminated Intravascular Coagulation, Fibrin Fibrinogen Degradation Products, Fibrinolysis, Placental Abruption

1. Introduction

Disseminated intravascular coagulation (DIC) is a severe condition characterized by systemic, marked coagulation activation and simultaneous fibrinolytic activation that leads to organ dysfunction and ultimately to death [1-3]. Four diagnostic scoring systems have been established to facilitate early treatment based on appropriate diagnosis of DIC. These systems were developed by the Japanese Ministry of Health and Welfare (JMHW) in 1988 [4], International Society on Thrombosis and Haemostasis (ISTH) in 2001 [3], Japanese Association for Acute Medicine (JAAM) in 2006 [5], and Japanese Society on Thrombosis and Hemostasis (JSTH) in 2017 [6]. For DIC diagnosis in obstetrics, the obstetrical DIC score was formulated in Japan in 1987 [7], and the pregnancy-modified ISTH (PM-ISTH) DIC score, applying the approach from the ISTH score for pregnant women, was developed in 2014 [8].

Asakura et al. [9, 10] emphasized the importance of DIC type classification based on the underlying pathology. Markedly activated coagulation is a major pathogenetic factor in all DIC types. The degree of fibrinolytic activation, however, differs depending on the underlying disease, which is an important factor in characterizing DIC [9, 10]. The JSTH system, based on the concept, proposed three clinical types of DIC: “infectious type” due to suppressed fibrinolysis, “hematopoietic disorder type” due to enhanced fibrinolysis, and “basic type” representing balanced fibrinolysis [6]. Hematopoietic disorder type DIC is typically seen in acute promyelocytic leukemia and some obstetrical diseases, including placental abruption [10]. Marked fibrinolytic activation in this type of DIC results in serious bleeding as a clinical symptom and extremely high levels of fibrin/fibrinogen degradation products (FDP) values seen in laboratory tests [1, 2, 9, 10]. Considering this DIC pathogenesis, FDP is an essential item for diagnosing DIC in obstetrics, and its threshold criteria should be higher than the FDP value for diagnosing DIC with an underlying infection or cancer [9, 10]. The FDP threshold criteria of the obstetrical DIC score in Japan, however, is as low as 10 μg/ml [7], and the PM-ISTH score does not incorporate FDP as a diagnostic item. No data are currently available on specific FDP criteria for diagnosis of hematopoietic disorder type DIC in obstetrics [11].

To address the above problem concerning FDP criteria in DIC diagnosis in obstetrics, Miyagi et al. [12] reported FDP and fibrinogen criteria reflecting the degree of coagulation activity. This was determined by the quantitative relation between the distributions of FDP and fibrinogen as shown by artificial intelligence using data from our previous publication [13], on women who incurred massive bleeding during delivery. The present study aimed to compare the current standard of existing DIC diagnostic scoring systems with the DIC diagnostic ability of revised versions to which our novel FDP threshold criteria from Miyagi et al. [12] were applied. In this way, we are able to assess and discuss the usefulness of our novel proposed FDP values [12].

2. Materials and Methods

This was a retrospective observational study, in which the participants were all women who gave birth at Okayama Medical Center (Okayama, Japan). We searched the Center’s database to identify all pregnant women who had been diagnosed with placental abruption between January 2008 and December 2020. We determined DIC diagnosis using four categories with reference to clinical diagnosis of DIC [8], which is consistent with the pathogenesis of hematopoietic disorder type DIC because of enhanced fibrinolysis seen in placental abruption [9, 10]: (1) plasma fibrinogen level <100 mg/dl [9, 14], (2) hemorrhage amount at delivery ≥2000 g [15], (3) both transfusion of red cell concentrate and fresh frozen plasma, and (4) renal dysfunction [16, 17] (exceeding the upper limits in both serum creatinine and blood urea nitrogen). We diagnosed cases fulfilling all four categories as true-DIC, and cases fulfilling categories 1–3 as sub-DIC, as organ symptoms are usually not seen in this type of DIC [9, 10]. We then compared laboratory and clinical data between the two groups.

We previously reported the fibrinogen criterion anticipated existence of coagulopathy as 237 mg/dl in pregnant women with massive bleeding during delivery [12]. In the present study, cases with coagulopathy (fibrinogen level <237 mg/dl) that did not meet the diagnostic criteria for true-DIC or sub-DIC were defined as a localized coagulopathy group, as proposed by Collis et al. [15]. We additionally placed cases with fibrinogen level ≥237 mg/dl into a non-coagulopathy group.

Based on Miyagi et al. [12], we defined the threshold criterion of a normal upper limit for FDP as 20 μg/ml. Miyagi et al. [12] additionally reported that when the FDP level increased by >85.1 μg/ml, the coagulation system would be substantively beyond a state of homeostasis. As 80 μg/ml was the upper limit in FDP laboratory test results at our hospital during the study period, we set 80 μg/ml as the criterion for marked increase of FDP in this study. We statistically determined the criterion for a moderate increase of FDP as 32 μg/ml, from 75th percentile values of FDP data used in our previous report [12], distributed in the range with fibrinogen levels >237 mg/dl, wherein coagulation system homeostasis was maintained.

We prepared the revised DIC diagnostic scoring systems by applying the novel FDP criteria determined as above, which were higher than in the existing current standards for each current system version (Table 1). The fibrin-related marker criteria of the ISTH current version [3] are categorical variables, though we could set concrete numerical values by applying the novel FDP criteria. For the JMHW [4] and JAAM [5] scoring systems, the diagnostic ability for DIC in placental abruption was compared using both the current version and the revised version applied the novel FDP values. For the ISTH system [3], wherein FDP items are categorical

variables, the revised version applying the FDP criteria was used for comparison. We made diagnosis of DIC by scoring up to four blood test results for each patient, using the current and revised version for each diagnosis. If any of the blood tests performed satisfied the scoring system for DIC, the case was diagnosed as DIC. For the PM-ISTH score [8], which excluded FDP as a diagnostic item, the current standard was used for comparison. The JSTH system [6] could not be examined in this study because that system includes coagulation activation-associated molecular markers (e.g., thrombin-antithrombin complex) that had not been measured in the study population. The obstetrical DIC score [7], which includes many clinical symptoms and laboratory data for diagnostic items, could not be examined in this study because of difficulty collecting accurate information for score calculation.

We used the Kruskal–Wallis test, Wilcoxon rank-sum test, and proportion test for statistical analysis, with P <0.05 set as the level of significance. This study was approved by the Institutional Review Board of Okayama Medical Center (IRB No. 2021–102) and conducted in accordance with the Declaration of Helsinki. The study was carried out with explanations provided to the patients, along with a website offering additional information, including an opt-out option.

Table 1. *Application of novel fibrin/fibrinogen degradation product (FDP) criteria to each disseminated intravascular coagulation (DIC) scoring system.*

Scoring system	FDP criteria (μg/ml) and points			
	Current version		Revised version	
JMHW	≥10 <20	1	≥20 <32	1
	≥20 <40	2	≥32 <80	2
	≥40	3	≥80	3
JAAM	<10	0	<20	0
	≥10 <25	1	≥20 <80	1
	≥25	3	≥80	3
ISTH	moderate increase	2	≥32 <80	2
	strong increase	3	≥80	3
PM-ISTH	N.A.		N.A.	

The revised version of the DIC diagnostic scoring system was prepared by applying our novel proposed FDP criteria [12] to each current version. ISTH, International Society on Thrombosis and Haemostasis; JAAM, Japanese Association for Acute Medicine; JMHW, Japanese Ministry of Health and Welfare; PM-ISTH, pregnancy-modified ISTH DIC score; N.A., not available.

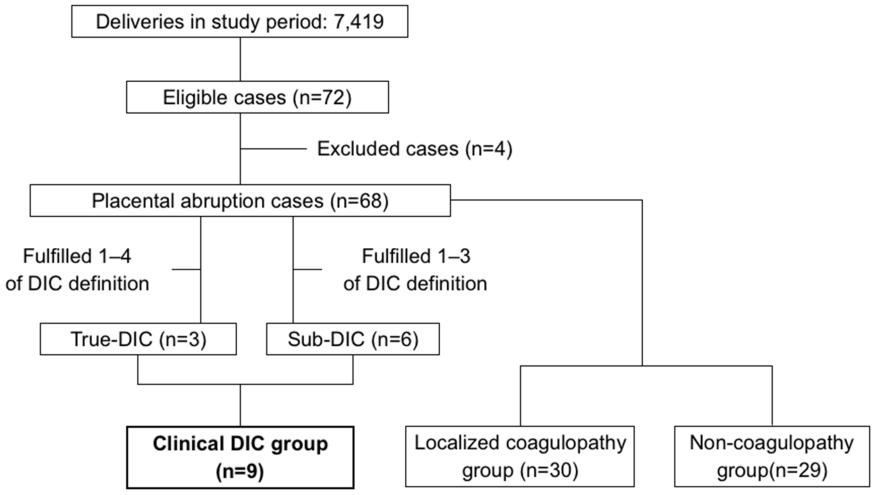

Figure 1. *Study participant flowchart.*

The categories for disseminated intravascular coagulation (DIC) diagnosis in this study are: (1) plasma fibrinogen level <100 mg/dl, (2) hemorrhage amount at delivery ≥2000 g, (3) blood product (red blood cells and fresh frozen plasma) transfusion, and (4) renal dysfunction.

3. Results

During the study period, 72 women with singleton pregnancies were eligible among 7,419 deliveries. Of these women, four were excluded because of incorrect diagnosis identified after reviewing their medical records. The final sample included 68 women with placental abruption; with a true-DIC (n=3) and sub-DIC (n=6) group. Comparison of laboratory and clinical data between the two groups showed no statistical differences for each item (data not shown); therefore the nine women from the two groups were considered as a clinical DIC group (Figure 1).

We classified a localized coagulopathy group (n=30) and non-coagulopathy group (n=29) per the definition in this study (Figure 1). Table 2 shows the laboratory and clinical data for the three examined groups. The clinical DIC group showed greater deterioration than the other two groups. The median FDP levels in the clinical DIC and localized coagulopathy groups were high, at >80 μg/ml, though the level was 30.5

μg/ml for the non-coagulopathy group. The complication rate of intrauterine fetal death in the clinical DIC group was 66.7%, the highest among the three groups (P <0.01).

Incidence of placental abruption for all deliveries was 0.92% during the study period, and occurrence of clinical DIC as defined in this study was observed in 13.2% of the placental abruption cases. Incidence of hypofibrinogenemia <237 mg/dl including clinical DIC in placental abruption was 57.4%.

Table 3 shows the sensitivity and specificity of the current and revised versions of the DIC scoring systems. Sensitivity was 1.00 in all four. The sensitivity and specificity of the JMHW system were excellent, at 1.00 and 0.864, respectively, in both versions. Those of the current version of the JAAM system were 1.00 and 0.678, respectively, while the revised version showed improved specificity of 0.797. The specificity for both the JMHW and ISTH revised versions was higher than for the JAAM current version (P <0.05) and PM-ISTH current version (P <0.0001).

Table 2. *Comparison of laboratory data and clinical data among three groups.*

Fibrinogen criteria (mg/dl)	Clinical DIC group (n=9)	Localized coagulopathy group (n=30)	Non-coagulopathy group (n=29)	*P*-value
	<100	<237	≥237	
Fibrinogen (mg/dl)	80 (30–80)	173 (25–230)	394 (256–465)	<0.0001
PT–INR	2.62 (1.62–4.47)	1.17 (0.91–3.1)	1.03 (0.85–1.23)	<0.0001
Hemoglobin (g/dl)	5.0 (3.6–8.2)	8.0 (4.4–10.5)	9.7 (6.2–13.8)	<0.0001
Platelet (×1000/μl)	41 (30–72)	136 (45–216)	201 (139–378)	<0.0001
FDPs (μg/ml)	80 (80–120)	80 (23.7–120)	30.5 (3.7–80)	<0.001
Hemorrhage amount (g)	2870 (2100–4435)	1030 (340–2456)	652 (80–1880)	<0.0001
Apgar score at 1 min	0 (0–1)	1.5 (0–7)	5 (0–9)	<0.0001
Cases complicated with IUFD (%)	6 (66.7)	6 (20.0)	3 (10.3)	<0.01

The placental abruption cases were classified into a clinical DIC group, localized coagulopathy group, and non-coagulopathy group by fibrinogen values. There were significant differences for the items in the first column among the three groups. Data are given as median (range) or number (%). DIC, disseminated intravascular coagulation; FDPs, fibrin/fibrinogen degradation products; INR, international normalized ratio; IUFD, intrauterine fetal death; PT, prothrombin time.

Table 3. *Sensitivity and specificity of current and revised version of each scoring system for disseminated intravascular coagulation (DIC) diagnosis in placental abruption.*

Scoring system	Diagnostic ability	Current version	Revised version
JMHW	Sensitivity	1.00	1.00
	Specificity	0.864	0.864
JAAM	Sensitivity	1.00	1.00
	Specificity	0.678	0.797
ISTH	Sensitivity	N.A.	1.00
	Specificity		0.864
PM-ISTH	Sensitivity	1.00	N.A.
	Specificity	0.424	

The revised version of the DIC diagnostic scoring system was prepared by applying our novel proposed FDP criteria [12] to each current version. The specificity of both the JMHW and ISTH revised versions was higher than that of the JAAM current version (P <0.05) and PM-ISTH current version (P <0.0001). ISTH, International Society on Thrombosis and Haemostasis; JAAM, Japanese Association for Acute Medicine; JMHW, Japanese Ministry of Health and Welfare; PM-ISTH, pregnancy-modified ISTH DIC score; N.A., not available.

4. Discussion

The results showed that our proposed FDP value may be useful as FDP threshold criteria when diagnosing DIC in placental abruption, which is a typical underlying disease of DIC in obstetrics [7, 10, 14]. In this study, applying the FDP criteria improved the diagnostic ability of the JAAM scoring system, and the ISTH and JMHW systems showed the same strong diagnostic ability. As the specificity of the PM-ISTH score, which excludes FDP in the diagnostic items, was the lowest, we deemed it necessary to incorporate FDP into the diagnostic items for DIC diagnosis in obstetrics.

FDP or D-dimer is recognized as an essential marker for DIC diagnosis [1, 2, 10, 11] based on the pathogenesis, and these are included as a diagnostic item in all DIC scoring systems [3-7] except for the PM-ISTH score [8]. Plasminogen activator inhibitor-1 (PAI-1) controls the degree of fibrinolytic activation in DIC [10, 18, 19]. As PAI-1 is scarcely elevated in enhanced-fibrinolytic-type DIC seen in placental abruption [10], plasmin activity increased, resulting in enhanced primary fibrinolysis and a greater increase of FDP compared with D-dimer. We therefore focused on FDP among fibrin-related markers in this study. Erez et al. [8] stated that fibrin-related markers such as FDP and D-dimer have low diagnostic value in pregnancy because this is a period when their baseline values are higher; therefore, they did not adopt fibrin-related markers as a diagnostic item in the PM-ISTH score. In fact, one report on healthy Chinese women indicated that FDP values for pregnant women in the third trimester were higher, though only slightly, than for non-pregnant women; the median and 25th–75th percentile values were 3.64 and 2.50–5.28 μg/ml for the former and 1.13 and 0.05–1.53 μg/ml for the latter [20]. In pathological conditions such as postpartum hemorrhage, however, despite the pathogenesis not being DIC, FDP has been reported to rise to quite high

levels (8–32 μg/ml), reflecting increased intravascular coagulation for hemostasis [21]. The FDP levels in postpartum hemorrhage are comparable with the FDP criteria for the DIC scoring systems by JMHW [4] and JAAM [5], which were not developed for assessing pregnant women. This supports the concept that DIC scoring systems in obstetrics need specific FDP criteria.

Miyagi et al. [12] reported that when fibrinogen is <237 mg/dl, the existence of coagulopathy should be considered by analyzing FDP's distribution function, using artificial intelligence based on the relationship between fibrinogen and FDP. We additionally performed statistical analysis of FDP data with fibrinogen in the normal range (≥237 mg/dl), and determined the threshold criteria as described above. Our novel proposed FDP threshold criteria [12] were established using patients with massive hemorrhage during delivery; therefore, these criteria appeared suitable for DIC diagnosis in obstetrics. The ISTH scoring system stated the cutoff values for "severely" or "moderate" elevated results of fibrin-related markers such as soluble fibrin monomers and FDP must be established based on the type of test used, as discussed in Taylor et al. [3], though that study did not mention concrete numbers for each marker. It is notable that we were able to replace this categorical variable with a scientifically based value for diagnosis of DIC in placental abruption.

The JMHW system's specificity did not change and showed favorable values when the novel FDP criteria were applied. A viable reason is the JMHW system is known to be excellent at DIC diagnosis for hematological diseases [10], while DIC in placental abruption is classified as an enhanced fibrinolysis type DIC, as with hematological diseases. As the ISTH system was partly developed based on the JMHW system [3], it is reasonable that the revised ISTH showed good specificity. The lack of fibrinogen in the diagnostic items and the low standard setting for FDP may have contributed to the low specificity (0.678) in the current JAAM system, designed to diagnose DIC in critically ill patients with trauma and sepsis [5]. Together with the poorest specificity (0.424) seen in the PM-ISTH score, which excluded FDP in the diagnostic items, the results indicate that high FDP and low fibrinogen levels are necessary for DIC diagnosis in placental abruption.

This study does have a few limitations. First, the number of clinical DIC cases in this study was small. We consider that this is a pilot study and the usefulness of the novel FDP criteria should be verified in the future. Second, the JAAM system includes the systemic inflammatory response syndrome (SIRS) score [22] for diagnosing sepsis – comprising respiratory rate, pulse rate, body temperature, and white blood cell count – as a diagnostic item. As this was a retrospective study, we could not collect exact physiological parameters, and therefore could not use the SIRS score in calculating the JAAM score. In this study, however, which focused on placental abruption rather than sepsis, we consider that the lack of SIRS score did not affect the JAAM score results. Another limitation was the absence of a completely objective diagnostic standard for DIC. This, however, is a common problem in research on DIC in pregnancy [14]. The concept of clinical diagnosis of DIC referred to in this study comprises severe maternal hemorrhage associated with coagulopathy, and low fibrinogen concentrations that require blood product transfusion [8]. The definition of DIC in this study was determined by using this concept, which is a viable reflection of the pathogenesis of enhanced fibrinolysis type DIC [9, 10]. Incidence of DIC in placental abruption as defined in this study was 13.2%, consistent with previous reports [23-25], and the laboratory findings for the clinical DIC group were extremely poor compared with the other two groups. We consider DIC as defined in this study to be acceptable.

5. Conclusion

This pilot study indicated that our novel proposed FDP criteria is potentially useful in diagnosing DIC in placental abruption. It is difficult to efficiently diagnose all aspects of DIC with a single diagnostic scoring system, and further studies are should be conducted to establish more useful diagnostic criteria for each laboratory test for diagnosing DIC in obstetrics. This study's strength is that it let us provide a rationale for adopting our novel proposed FDP criteria to future studies.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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