Consumptive Coagulopathy Involving Amniotic Fluid Embolism: The Importance of Earlier Assessments for Interventions in Critical Care

Tomoaki Oda, MD, PhD; Naoaki Tamura, MD, PhD; Rui Ide, MD; Toshiya Itoh, MD;
Yoshimasa Horikoshi, MD; Masako Matsumoto, MD, PhD; Megumi Narumi, MD, PhD;
Yukiko Kohmura-Kobayashi, MD, PhD; Naomi Furuta-Isomura, MD, PhD; Chizuko Yaguchi, MD, PhD;
Toshiyuki Uchida, MD, PhD; Kazunao Suzuki, MD, PhD; Hiroaki Itoh, MD, DMedSci;
Naohiro Kanayama, MD, PhD

Objectives: Amniotic fluid embolism is a rare disease that induces fatal coagulopathy; however, due to its rarity, it has not yet been examined in detail. The strict diagnostic criteria by Clark for amniotic fluid embolism include severe coagulopathy complicated by cardiopulmonary insufficiency, whereas the Japanese criteria also include postpartum hemorrhage or Disseminated Intravascular Coagulation in clinical practice. Amniotic fluid embolism cases with preceding consumptive coagulopathy may exist and are potential clinical targets for earlier assessments and interventions among amniotic fluid embolism cases fulfilling the Japanese, but not Clark criteria. The present study was performed to compare coagulopathy in the earlier stage between the amniotic fluid embolism patients diagnosed by Clark criteria (Clark group, $n = 6$), those by the Japanese criteria (Non-Clark group, $n = 10$), and peripartum controls and identify optimal clinical markers for earlier assessments of amniotic fluid embolism-related consumptive coagulopathy.

Design: Retrospective case-control study.

Setting: A single university-based center. Our amniotic fluid embolism registry program has accumulated clinical information and blood samples since 2003.

Patients: Amniotic fluid embolism patients in the Clark and Non-Clark groups between 2009 and 2017 and peripartum controls.

Interventions: None.

Measurements and Main Results: Clinical information was collected on hemoglobin levels, platelet counts, and coagulation- and fibrinolysis-related variables. Fibrinolytic parameters were also measured and compared among the three groups before blood transfusion. Fibrinogen levels in all patients in the Clark group and most in the Non-Clark group decreased earlier than hemoglobin levels, which was consistent with the high hemoglobin/fibrinogen ratio and, thus, is a promising clinical marker for the earlier assessment of amniotic fluid embolism-related consumptive coagulopathy.

Conclusions: Earlier evaluations of consumptive coagulopathy and hyperfibrinolysis using the hemoglobin/fibrinogen ratio following preemptive treatment may reduce the occurrence or prevent the aggravation of severe coagulopathy in amniotic fluid embolism patients. (*Crit Care Med* 2020; 48:e1251–e1259)

Key Words: amniotic fluid embolism; blood coagulation; Disseminated Intravascular Coagulation; fibrinolysis; pregnancy

Amniotic fluid embolism (AFE) is a rare disease that is associated with high maternal and/or fetal morbidity and mortality rates (1). It is mainly characterized by the abrupt onset and rapid progression of maternal cardiopulmonary insufficiency, concomitant with Disseminated Intravascular Coagulation (DIC). Its histopathological diagnosis has been classically defined (2), that is, detection of fetal components in pulmonary vessels; however, this is only applicable in fatal cases examined by autopsy and not in surviving cases. A consensus of clinical diagnostic criteria has not been universally established, and different diagnostic criteria for AFE have been reported worldwide (3–7). The diagnostic criteria reported by Clark et al (8) (Clark criteria) were originally employed in an attempt to establish uniform criteria for research with strictly defined symptoms and conditions; however, they do not include strongly suspected clinical cases with missing coagulation data supporting overt DIC (9). The criteria

were recently evaluated and validated by Stafford et al (10). Previous case reports (11, 12) suggested that cardiopulmonary insufficiency and refractory DIC have already advanced in patients clinically diagnosed with AFE by Clark criteria, and thus, the opportunity for earlier preemptive interventions and a better prognosis is missed. The onset of AFE generally occurs in the delivery room, in which human resources for critical care are more limited than that in an ICU. Under these conditions, blood transfusions, hemostatic interventions, and maternal life-support are often performed before the evaluation of coagulopathy, as recommended by some obstetric guidelines (13, 14), which may be one of the major factors compromising detailed analyses of coagulopathy in AFE.

In the present study, we assumed that preceding severe consumptive coagulopathy may aggravate not only dilutional coagulopathy after massive bleeding but cardiopulmonary insufficiency in some patients diagnosed with AFE by Clark criteria, based on previous case reports (11, 12). We also expected the phase of preceding consumptive coagulopathy to represent an optimal opportunity for preemptive interventions to improve maternal and fetal prognoses. We focused on the Japanese diagnostic criteria for AFE (3), which have been widely used in Japanese clinical practice. These criteria may also be applicable to the cases of DIC or severe bleeding, even if cardiopulmonary insufficiency is not observed; therefore, all AFE patients diagnosed by Clark criteria were expected to be included among those diagnosed by the Japanese criteria (**Fig. 1***A*). We hypothesized that severe consumptive coagulopathy occurs before dilutional coagulopathy due to massive bleeding and/or cardiopulmonary insufficiency in patients with AFE diagnosed by the Japanese criteria. These patients fulfill the Japanese AFE criteria but not Clark criteria, and may
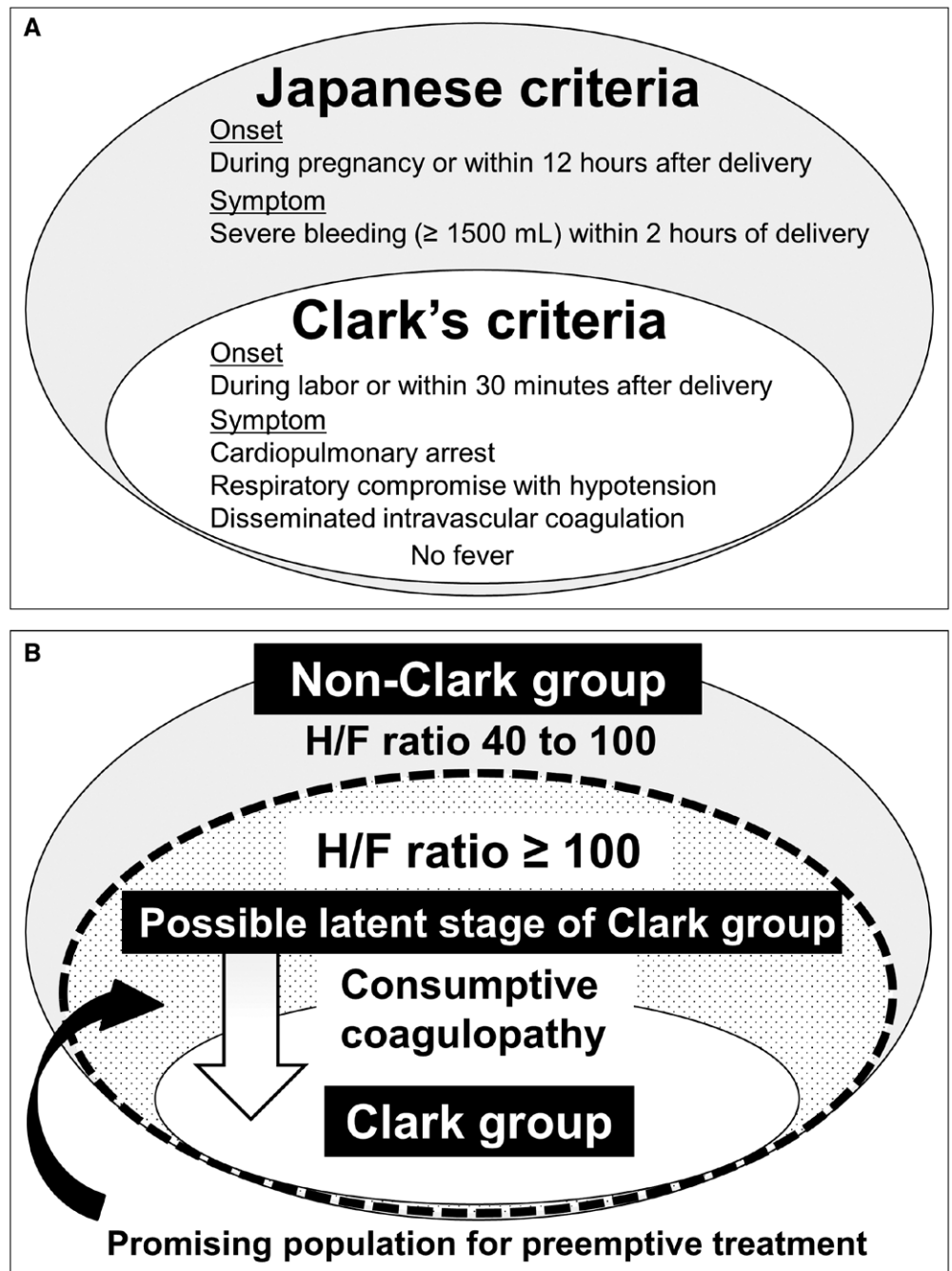

Figure 1. Categorization of amniotic fluid embolism (AFE) by the Japanese and Clark's criteria (**A**) and a new proposal of the possible latent stage of Clark group (**B**). **A**, The relationship between the Japanese and Clark diagnostic criteria for AFE and the definition of AFE groups in the present study. Regarding symptoms, Clark criteria strictly require cardiopulmonary arrest or respiratory compromise with hypotension in addition to disseminated intravascular coagulation (DIC), whereas the Japanese criteria diagnose AFE based on only one of four symptoms (i.e., severe bleeding of more than 1,500 mL, cardiac arrest, respiratory failure, and DIC). In the present study, AFE patients were classified into two groups: AFE (Clark) (the population in the *white part*) and AFE (Non-Clark) (that in the *gray part*). **B**, The scheme representing a promising population for preemptive treatment using the hemoglobin (H)/fibrinogen (F) ratio among Non-Clark group. The Non-Clark AFE group included a population complicated by preceding consumptive coagulopathy, which may develop cardiopulmonary insufficiency; in other words, "the possible latent stage of the Clark group," in consideration of previous case reports (11, 12). The identification of these potential Clark group patients by referring to the Japanese criteria in combination with an H/F ratio of more than 100 may enable physicians to provide preemptive treatments in the earlier stage, which may prevent fatal AFE.

be clinical targets for earlier assessments and interventions in critical care. Therefore, the aim of the present study was to compare coagulopathy between the AFE patients fulfilling Clark criteria (Clark group, $n = 6$), those fulfilling the Japanese, but not Clark criteria (Non-Clark group, $n = 10$) before any blood transfusion, and peripartum controls in order to identify optimal clinical markers for earlier assessments.

MATERIALS AND METHODS

AFE Diagnosis and Classification

AFE patients were grouped according to the Clark and Japanese diagnostic criteria. The former originally aims to establish uniform criteria for research reporting and includes cardiopulmonary compromise with overt DIC during labor or within 30 minutes of delivery (8) (**Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F846). DIC scores defined by Clark et al (8) are calculated using the platelet count, prothrombin time-international normalized ratio (PT-INR), and fibrinogen level. Patients diagnosed using the Japanese criteria (3) have the following symptoms that developed during pregnancy or within 12 hours of delivery: 1) cardiac arrest, 2) severe bleeding of unknown origin within 2 hours of delivery ($\geq$ 1,500 mL), 3) DIC, or 4) respiratory failure (3) (**Table S2**, Supplemental Digital Content 2, http://links.lww.com/CCM/F847). DIC is mainly diagnosed in Japan using the obstetrical DIC score (15, 16). Three different DIC diagnostic scores are described in **Table S3** (Supplemental Digital Content 3, http://links. lww.com/CCM/F848): 1) the Modified International Society on Thrombosis and Haemostasis (ISTH)-DIC score reported by Clark (8), 2) the Japanese Obstetrical DIC score (15, 16), and 3) the Japanese Association for Acute Medicine (JAAM) DIC score (17), one of the more common scoring systems for DIC. Both Clark and the Japanese diagnostic criteria exclude AFE when findings or symptoms may be attributed to other diseases. In the present study, we defined "AFE (Clark)" as AFE patients in the Clark group and "AFE (Non-Clark)" as those in the Non-Clark group. AFE patients (Clark) were expected to be included among those diagnosed by the Japanese diagnostic criteria (Fig. 1*A*).

Patients

Since our university launched the Japanese AFE registry program in 2003, clinical information and blood specimens have been delivered to our university for the analysis of AFE (3). When clinicians suspected AFE, they were recommended to collect serum and/or plasma from patients during the clinical course, which were then processed in each hospital and delivered frozen (–30°C) to our university with written informed consent. Among 1,482 patients with 1,944 blood samples collected between 2009 and 2017, only 16 plasma specimens were collected before blood transfusion and still currently available. We examined clinical information as well as coagulation and fibrinolysis parameters, and classified patients into AFE (Clark) or AFE (Non-Clark). As a control, we also measured the following parameters using plasma

specimens collected at the three peripartum stages: before labor, during labor, and postpartum until 30 hours from delivery, among singleton pregnancies without complications involving platelets, blood coagulation, or postpartum hemorrhage. In the present study, postpartum hemorrhage was defined as estimated blood loss of more than 800 and 1,500 mL in vaginal and cesarean deliveries, respectively, as reported in the Japanese practice guidelines (13).

Data Collection and Measurement of Fibrinolytic Parameters

We collected data on hemoglobin levels, hematocrits, platelet counts, fibrinogen levels, PT-INR, fibrin(ogen)-degradation products (FDPs), and D-dimer in all groups. In the present study, we focused on the discrepancy between the hemoglobin and fibrinogen levels at the onset of AFE according to the following reasons. First, coagulopathy of AFE potentially developed systemic hemorrhage, which resultantly led to anemia; however, the patient's hemoglobin concentration was often maintained before bleeding and/or even immediately after acute hemorrhage, as previously reported (18, 19). Second, on the other hand, fibrinogen levels in AFE frequently decreased in a remarkably short length of time from the onset (20). Third, elevated FDP, D-dimer, and tissue plasminogen activator were reported in the previous AFE case report (21), which suggested that hyperfibrinolysis might further aggravate decrease of fibrinogen levels at least in some cases of AFE. Fourth, therefore, an increased ratio of the case's hemoglobin concentration divided by the fibrinogen level could be indicative of severity of consumptive coagulopathy. The hemoglobin (H)/fibrinogen (F) ratio was calculated as hemoglobin (g/L) divided by fibrinogen (g/L). It would be noted that microangiopathic hemolysis might potentially affect the H/F ratio and should be excluded carefully.

We also measured the following variables in plasma specimens: plasmin-$\alpha2$ plasmin inhibitor complex (PIC; LPIA-ACE PPI II, LSI Medience, Tokyo, Japan), elastase XDP (E-XDP, LSI Medience, Tokyo, Japan) (cross-linked fibrin degradation products), that is, FDP of neutrophil elastase, and neutrophil elastase (INNOTECH Elastase, Sanwa Kagaku Kenkyusho, Nagoya, Japan). PIC measures the amount of plasmin, which is a major fibrinolytic enzyme in blood. E-XDP assay measures the fibrin(ogen) fragments created by the action of neutrophil elastase. We measured FDP (Nanopia P-FDP, Sekisui Medical, Tokyo, Japan) and D-dimer (LATECLE D-dimer, KAINOS, Tokyo, Japan) when clinical information delivered to our university from the hospitals in charge did not include these data. FDP includes FDPs by plasmin and neutrophil elastase, whereas D-dimer is a product of fibrin cleaved by plasmin. In patients in whom values were above or below the threshold of the assay, we described each threshold with signs of inequality or "undetectable," as reported by physicians. Every assay was performed by SRL, Tokyo, Japan.

Statistical Analysis

All continuous data were expressed as the median with a minimum to maximum. Statistical analyses included Fisher exact

test or the chi-square test for categorical data. Continuous data were evaluated by the Mann-Whitney *U* test between two groups and by a Kruskal-Wallis analysis followed by Dunn multiple comparison test among three groups. Spearman correlation analysis was used to examine the relationship between each two parameters. A two-sided *p* value less than 0.05 was defined as being significantly different. *p* values were adjusted to account for multiple comparisons. GraphPad Prism Version 7 (GraphPad Software, San Diego, CA) was used for statistical calculations. The Institutional Review Board at the Hamamatsu University School of Medicine approved the present study (Numbers 15-333 and 16-165) with written informed consent by patients.

RESULTS

Sixteen patients were classified into the AFE (Clark) group (*n* = 6) and the AFE (Non-Clark) group (*n* = 10). AFE (Clark) had two fatal maternal cases. The control group included 44 patients with plasma specimens that were collected before labor (*n* = 18), during labor (*n* = 13), and postpartum (*n* = 13). **Table 1** shows patient backgrounds. Patients in AFE (Clark) frequently developed cardiopulmonary insufficiency as the initial symptom. In contrast, most patients in AFE (Non-Clark) developed postpartum hemorrhage due to refractory uterine atony complicated by coagulopathy within 2 hours of delivery. Plasma from AFE patients was mostly collected within 1 hour of the onset, but before blood transfusions. **Table S4** (Supplemental Digital Content 4, http://links.lww.com/CCM/F849) shows hemoglobin levels, hematocrits, platelet counts, PT-INR, and fibrinogen levels with the clinical information of both AFE groups. All patients in AFE (Clark) had overt DIC along with its diagnostic criteria; nevertheless, most of their hemoglobin levels (66–136 g/L) and hematocrits were maintained contrary to low fibrinogen levels (below 1.51 g/L) and prolonged PT-INR, which is resulting in a high H/F ratio of more than 100. On the other hand, many patients in AFE (Non-Clark) had significant bleeding, which may have contributed to their low hemoglobin levels (10–91 g/L) and hematocrits as well as decreased blood coagulation function (below 1.69 g/L in fibrinogen levels), so-called "dilutional coagulopathy"; therefore, their calculated H/F ratios ranged between 40 and 100.

AFE (Clark) and AFE (Non-Clark) both had significantly higher PIC, FDP, and D-dimer than the control group; however, no significant differences were observed between the two AFE groups. Neutrophil elastase and E-XDP were significantly higher in AFE (Clark) than that in the control group (**Fig. S1**, Supplemental Digital Content 5, http://links.lww.com/CCM/F850). Postpartum control patients had significantly higher PIC and FDP than those before and during labor, as well as higher D-dimer and neutrophil elastase than those before labor (data not shown); however, the increases observed in these parameters were smaller than those in AFE patients. All H/F ratios were less than 40 in peripartum controls but increased to more than 40 in two AFE groups with no significant difference (**Fig. 2A**). When AFE patients in the present study were classified by H/F ratios between 40 and 100 as cutoffs, most patients in the Clark group and one-third in the Non-Clark group were assigned to an H/F ratio of more than 100 (Table S4, Supplemental Digital Content 4, http://links.lww.com/CCM/F849), which indicates that one-third of the patients with AFE (Non-Clark) have a potential of severe consumptive coagulopathy similar to those with AFE (Clark). The H/F ratio negatively and positively correlated with fibrinogen levels ($\rho = -0.91$, $p < 0.0001$) and PT-INR ($\rho = 0.65$, $p < 0.0001$) (**Fig. 2**, **B** and **C**), respectively; it also positively correlated with the present fibrinolytic parameters, PIC ($\rho = 0.54$, $p < 0.001$), and D-dimer ($\rho = 0.59$, $p < 0.001$) (**Fig. 2**, **D** and **E**). The serum parameters involving microangiopathic hemolysis were described in **Table S5** (Supplemental Digital Content 6, http://links.lww.com/CCM/F851). We could not deny a possible coexistence of microangiopathic hemolysis in two of the 16 AFE cases. When the H/F ratio and its cutoff were more frequently applied to obstetric hemorrhage before blood transfusion, patients with an H/F ratio of more than 100 had severe coagulopathy despite a rather small amount of bleeding, whereas those with H/F ratios between 40 and 100 frequently had reduced hemoglobin and fibrinogen levels concomitant with considerable blood loss (**Table 2**).

DISCUSSION

The present results revealed that some patients with AFE (Non-Clark) had specific coagulopathy that coincided with hyperfibrinolysis at the onset. Coagulopathy was characterized by a discrepancy between the maintained hemoglobin and markedly decreased fibrinogen levels, so-called "consumptive coagulopathy," which was common in all patients with AFE (Clark). We showed that the Non-Clark AFE population included some patients with preceding severe consumptive coagulopathy represented by an H/F ratio of more than 100, who potentially later develop not only refractory postpartum hemorrhage with coagulopathy but cardiopulmonary failure, based on the findings of previous case reports (11, 12). The specific population (three cases in 10 Non-Clark group in the present study) with severe consumptive coagulopathy before development of cardiopulmonary insufficiency among the Non-Clark group; in other words, "the possible latent stage of AFE (Clark)" are promising clinical targets for earlier assessments and interventions of consumptive coagulopathy in critical care (**Fig. 1B**).

The fundamental concept of consumptive coagulopathy, also described as DIC, is defined by the ISTH (22). Clinical obstetricians mainly appear to have the practical concept of consumptive coagulopathy as blood coagulation dysfunction with a small amount of blood loss to account for dilutional coagulopathy; nevertheless, its definition in obstetric practice has not yet been established (23). Therefore, practical difficulties are associated with reaching an early clinical diagnosis. Although some diagnostic scores of DIC (17, 22) are now available in critical care, these scoring systems do not consider obstetric cases. Pregnancy induces a specific procoagulant state that significantly alters coagulation and fibrinolysis parameters from those in nonpregnant women (23). The diagnostic scores for obstetric DIC reported by Clark et al (8) and Erez et al (24) require the platelet count, prothrombin time, and fibrinogen

TABLE 1. Patient Backgrounds

		Control Before Labor ($n = 18$) During Labor ($n = 13$) Postpartum ($n = 13$)	AFE Patients in the Clark Group ($n = 6$)	AFE Patients in the Non-Clark group ($n = 10$)	p
Age (yr)		33 (21–41)	34 (27–42)	34 (24–41)	0.92
Primipara (case)		19	3	5	0.90
Gestational age at delivery (d)		273 (257–289)	277 (203–292)	281 (254–291)	0.19
Mode of delivery (case)	Vaginal delivery	23	2	4	0.58
	Cesarean section	21	4	6	
Onset	During labor (case)	NA	4	1	< 0.05
	Postpartum (case)	NA	2	9	
	Time after delivery (min)	NA	16 (1–30)	60 (1–120)	0.40
Initial symptoms (case)	Respiratory compromise with hypotension	NA	2	1	0.52
	Cardiopulmonary arrest	NA	4	0	< 0.01
	Postpartum hemorrhage	NA	1	9	< 0.01
	Uterine atony	NA	1	7	0.12
Period of plasma collection		Before labor: 269 d (264–289 d) During labor: 277 d (267–288 d) First stage: $n = 12$ Second stage: $n = 1$ Postpartum: 18 hr (2–30 hr) after delivery	32 min (12–200 min) from the onset	60 min (13–90 min) from the onset	0.31[a]
Modified International Society on Thrombosis and Haemostasis disseminated intravascular coagulation score[b] (case)	Yes (3 or more)	NA	6	5	0.09
	No (less than 3)	NA	0	5	
Blood loss at plasma collection (mL)	Cases during labor	0	0 (0–1,500)	0	NA[c]
	Cases in postpartum	640 (175–800)	1,501 (740–2,262)	2,645 (1,300–4,800)	< 0.001[d]
Maternal outcome (case)	Survival	NA	4	10	0.13
	Death	NA	2	0	
Fetal outcome (case)	Survival	NA	5	10	0.38
	Death	NA	1	0	

AFE = amniotic fluid embolism, NA = not applicable.

[a]p value between the AFE Patients in the Clark Group and AFE Patients in the Non-Clark Group (AFE [Non-Clark]) groups.

[b]Calculation of modified International Society on Thrombosis and Haemostasis disseminated intravascular coagulation (DIC) scores and evaluation of overt DIC according to Clark et al (8).

[c]Statistical analyses were not performed due to the insufficient number ($n = 1$) of patients in the AFE (Non-Clark) group.

[d]Post hoc multiple comparisons showed a significant difference ($p < 0.001$) between control cases in postpartum and AFE (Non-Clark).

Sixteen AFE patients diagnosed by the Japanese criteria was classified into two groups, i.e., Clark group ($n = 6$) and Non-Clark group ($n = 10$).

level. Physicians also need to evaluate how many scores each parameter represents and obtain the sum of three scores. These complex steps to diagnose overt DIC may clinically result in a delay in the initiation of an appropriate intervention for severe cases. Furthermore, in the present study, all patients in AFE (Non-Clark) were diagnosed with DIC according to the
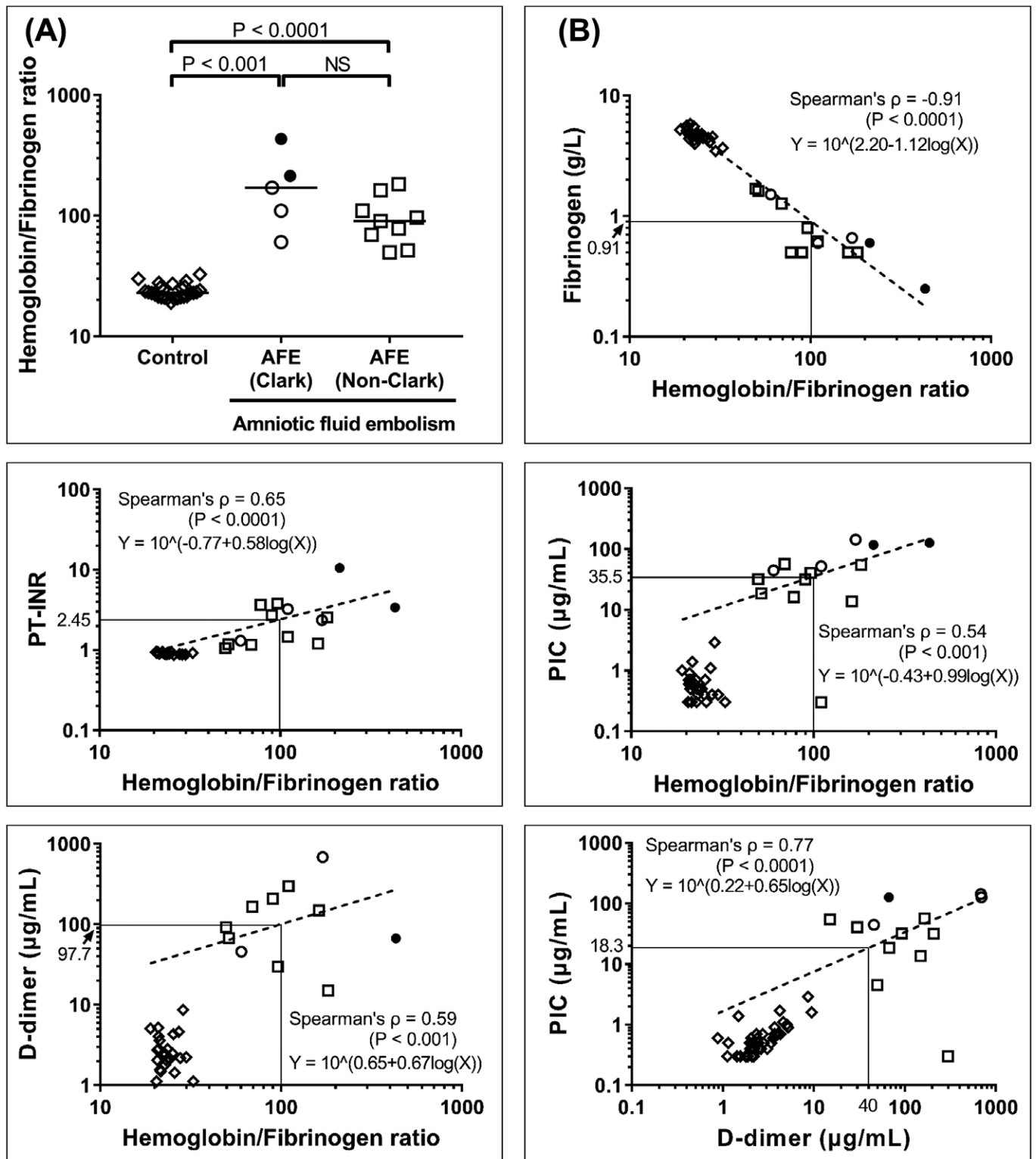
Figure 2. The hemoglobin (H)/fibrinogen (F) ratio with its related coagulation and fibrinolytic parameters among patients in the present study. **A**, The H/F ratio among patients in the present study. **B**, Correlation with fibrinogen levels. **C**, Correlation with prothrombin time-international normalized ratio (PT-INR). **D**, Correlation with plasmin-α2 plasmin inhibitor complex (PIC). **E**, Correlation with D-dimer. **F**, Correlation between D-dimer and PIC. *Circles*, *squares*, and *rhombi* indicate patients with amniotic fluid embolism (AFE) (Clark), AFE (Non-Clark), and peripartum controls, respectively. *Filled circles* represent fatal cases of AFE (Clark). Data on the H/F ratio were only available for 27 out of 44 control cases in (A)–(E). NS, not significant.

diagnostic scoring by Erez et al (24); however, 50% of this population were not considered to have overt DIC based on Clark criteria (8). This serious discrepancy in the diagnosis of DIC

may result in confusion in evaluations and treatments in critical practice. It is also important to note that these obstetric DIC scoring systems as well as the obstetrical DIC Score widely

TABLE 2. Backgrounds and Laboratory Data Before Blood Transfusion Among Patients With Obstetric Hemorrhage in Our Database: Classification by the Hemoglobin/Fibrinogen Ratio

		Group (A), Hemoglobin/ Fibrinogen Ratio Less Than 40 ($n = 17$)	Group (B), Hemoglobin/ Fibrinogen Ratio 40–100 ($n = 8$)	Group (C), Hemoglobin/ Fibrinogen Ratio 100 or More ($n = 8$)	p
Number of patients (case)	Previa and accreta	7	4	1	0.25
	Abruption	10	4	7 (5 intrauterine fetal death)	
Primipara (case)		9	5	3	0.60
Complicated by preeclampsia (case)		1	2	3	0.14
Gestational age (d)		257 (246–294)	246 (215–283)	223 (179–275)	$< 0.01^a$
Plasma collection time from the onset (min)		53 (7–240)	75 (0–257)	120 (30–300)	0.33
Blood loss at plasma collection (mL)		1,261 (0–3,500)	1790 (0–2,876)	40 (0–1,120)	0.08
Laboratory data	Hemoglobin (g/L)	88 (43–125)	78 (41–125)	104 (91–129)	$< 0.05^b$
	Platelet count ($\times 10^9$/L)	147 (67–420)	129 (77–249)	138 (77–202)	0.55
	Prothrombin time-international normalized ratio	1.06 (0.86–1.35)	1.20 (0.90–1.70)	1.20 (0.86–2.39)	0.09
	Fibrinogen (g/L)	3.09 (1.11–4.72)	1.51 (0.73–1.87)	0.70 (0.25–0.84)	$< 0.0001^c$
	D-dimer (µg/mL)	4.9 (1.7–132.2)	102 (8.4–596)	236 (50–1,829)	$< 0.001^d$
	Antithrombin (%)	61 (20–99)	46 (32–66)	75 (37–96)	0.06
Overt disseminated intravascular coagulation	Defined by Clark[e] (case)	2	2	4	0.11
	Defined by Erez[f] (case)	8	8	8	< 0.01

[a]Post hoc multiple comparisons showed a significant difference between (A) and (C) ($p < 0.01$).
[b]Post hoc multiple comparisons showed a significant difference between (A) and (C) ($p < 0.05$).
[c]Post hoc multiple comparisons showed a significant difference between (A) and (B) ($p < 0.05$) as well as between (A) and (C) ($p < 0.0001$).
[d]Post hoc multiple comparisons showed a significant difference between (A) and (B) ($p < 0.05$) as well as between (A) and (C) ($p < 0.001$).
[e]Overt disseminated intravascular coagulation (DIC) defined by Clark was evaluated according to Clark et al (8).
[f]Overt DIC defined by Erez was evaluated according to Erez et al (24).
Obstetric hemorrhage cases were classified as (A), (B), and (C) according to the Hemoglobin/Fibrinogen ratio.
Patients in group (C) maintained hemoglobin levels with a small amount of blood loss; however, fibrinogen levels markedly decreased and coincided with highly elevated D-dimer levels, which indicated severely disturbed blood coagulation function due to consumptive coagulopathy concomitant with hyperfibrinolysis. Blood loss may have partly caused decreased hemoglobin levels as a result of dilutional coagulopathy in some cases in group (B); nevertheless, the majority of patients also had critically low fibrinogen levels with elevated D-dimer levels. Overt DIC was diagnosed in only 50% of cases, even in group (C) with Clark criteria (8), whereas all cases in groups (B) and (C) were diagnosed with Overt DIC by Erez diagnostic criteria (24).

used in Japan (15, 16) identified DIC cases but did not evaluate the severity of coagulopathy. An H/F ratio of more than 100 could be indicative of preceding consumptive coagulopathy before massive bleeding. However, the fibrinogen levels decreased below the reported fibrinogen cutoffs (8, 24) in all of the current AFE cases (**Fig. S2**, Supplemental Digital Content 7, http://links.lww.com/CCM/F852), suggesting that a fibrinogen level alone may not always be useful to distinguish consumptive coagulopathy from dilutional one.

We herein proposed for the first time a clinically available index, the H/F ratio, which indicated severity of consumptive coagulopathy in the early phase of onset in AFE patients.

Furthermore, we propose a preemptive strategy of assessments and interventions for AFE based on the Japanese AFE criteria and H/F ratio shown in **Figure 3**. When patients have dyspnea, hypotension, impaired consciousness, or postpartum hemorrhage during labor or a few hours after delivery, AFE needs to be clinically differentiated from other critical diseases, such as pulmonary thromboembolism, peripartum cardiomyopathy, or intracranial hemorrhage, based on the Japanese AFE diagnostic criteria. In the case of cardiac arrest, cardiopulmonary resuscitation is the first priority; nevertheless, the following proposed second screening is recommended simultaneously during resuscitation or immediately after the return of spontaneous circulation, because
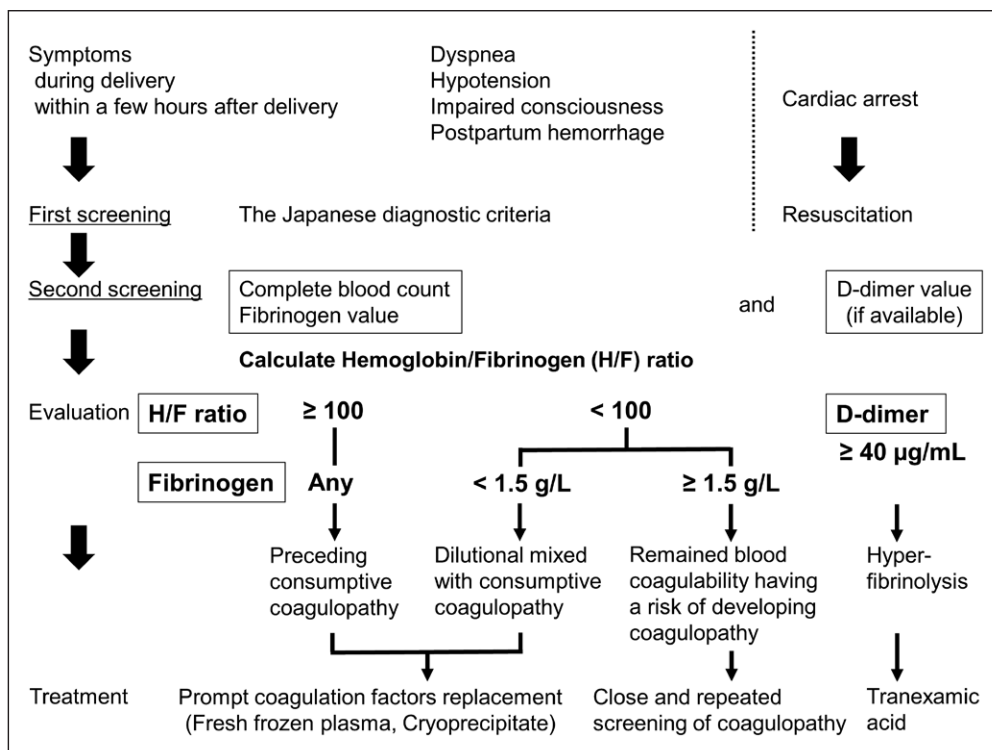
Figure 3. Proposed preemptive strategy for earlier assessments and interventions in the clinical practice of coagulopathy involving amniotic fluid embolism. When physicians clinically suspect the development of amniotic fluid embolism from symptoms based on the Japanese diagnostic criteria of amniotic fluid embolism, a complete blood count and the measurement of fibrinogen levels, as well as D-dimer levels if possible, are recommended. When the hemoglobin (H)/fibrinogen (F) ratio (both in g/L) is more than 100, or less than 100 in combination with a fibrinogen level lower than 1.5 g/L, physicians are encouraged to administer promptly coagulation factors with fresh frozen plasma or a cryoprecipitate. Patients with a D-dimer level of more than 40 may have hyperfibrinolysis, which is treated with tranexamic acid.

cardiac arrest, also recognized as one of the symptoms of AFE, and resuscitation induce hyperfibrinolytic DIC (25). We propose a complete blood count and measurement of fibrinogen levels, as well as D-dimer if possible, in the second screening. If the H/F ratio (both in g/L) is calculated as more than 100, which is evaluated as "preceding consumptive coagulopathy," physicians are encouraged to administer promptly coagulation factors with fresh frozen plasma or a cryoprecipitate. A calculated H/F ratio of less than 100 suggests that the patient is also affected by dilutional coagulopathy due to considerable bleeding. However, if the fibrinogen level is less than 1.5 g/L, the earlier replacement of blood coagulation factors is recommended according to the Japanese guidelines (13). Based on our previous report (26), earlier interventions with plasma-derived blood products might further inhibit an anaphylactoid reaction in the lungs and uterus (27, 28) effectively. On the other hand, repeated screening of blood coagulability is recommended when fibrinogen levels are maintained at more than 1.5 g/L, because patients may be at risk of further deteriorations in blood coagulation. However, the H/F ratio may not be accurately evaluated after transfusions with blood products due to modified hemoglobin and fibrinogen values. When patients are included in the first screening based on the Japanese AFE diagnostic criteria, those with D-dimer higher than 40, indicating highly elevated PIC (**Fig. 2F**), are considered to have hyperfibrinolysis, which may be treated with antifibrinolytic agents, such as tranexamic acid, a universally available antifibrinolytic

drug. Previously reported doses of tranexamic acid were between 1 and 2g based on the findings of large randomized control trials on postpartum hemorrhage (29) and severe trauma (30).

There were two main limitations in the present study. Many values were above or below thresholds (data not shown), which complicated exact statistical calculations. Therefore, we may have underestimated the severity of the coagulation disturbance. Although we examined 1,944 blood samples delivered to the Japan AFE registry in our institution between 2009 and 2017, the number of citrated plasma specimens before blood transfusion was only 16 out of 125 plasma samples during that period. It is important to note that these citrated plasma specimens, despite their small number, are significant considering the rarity of the disease.

CONCLUSIONS

We herein demonstrated that the majority of AFE patients defined by Clark criteria and some of those diagnosed by the Japanese diagnostic criteria had severe consumptive coagulopathy and hyperfibrinolysis at the onset. The new concept of the H/F ratio may be a concise and clinically useful index that indicates the severity of consumptive coagulopathy in the early stage of AFE. Earlier clinical evaluations of consumptive coagulopathy and hyperfibrinolysis with the H/F ratio may facilitate prompt preemptive treatment with coagulation factor replacement along with antifibrinolytic agents, which will prevent not only severe coagulopathy and its aggravation but sudden cardiopulmonary failure in some AFE patients.

ACKNOWLEDGMENTS

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