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Clinical Application of Coagulation Biomarkers

Makoto Aoki, Shuichi Hagiwara and
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Abstract

Coagulopathy is of intense interest in the fields of emergency medicine, with many recent studies of coagulation biomarkers for clinical use. The occurrence of disseminated intravascular coagulation (DIC) also resulted in the activation of studies about the coagulopathy. At present DIC has been admitted in many clinical conditions and many coagulation biomarkers have been studied. Fibrin degradation product (FDP) and D-dimer are one type of coagulation biomarker. A characteristic of FDP and D-dimer is the rapid and dynamic elevation of their levels when fibrinolysis occurs in several acute diseases. In this chapter, we present the clinical application of FDP and D-dimer. In trauma, FDP and -dimer have been used for the evaluation of trauma severity, to predict the likelihood of hemorrhage and to evaluate the need for the transfusion of packed red blood cells. In cardiac pulmonary arrest (CPA), FDP and D-dimer have been useful for predicting the return of spontaneous circulation. Thus, the measurement of coagulation biomarkers is useful in the diagnosis and/or treatment of trauma and CPA.

Keywords: fibrin degradation product, D-dimer, diagnosis, prognosis, emergency medicine

1. Introduction

Fine balance exists between coagulation and fibrinolysis within the coagulation system, with coagulopathy defined as the failure of this balance. Coagulopathy has long been known to occur in several acute diseases such as cardiovascular disease [1], infection [2] and trauma [3]. In response, coagulation biomarkers have been identified and used in clinical practice in recent years to diagnose and treat several diseases of the coagulation system.

There is a variety of coagulation biomarkers used in real clinical situation. Prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen has been used to test the coagulation function from long ago in hematologic disorder, liver disease, disseminated intravascular coagulation (DIC) and to monitor the use of anticoagulation drugs. Owing to the recent progress in measuring method, the more minute coagulation biomarkers can be measured and divided into coagulation systems and fibrinolytic systems. Each example is thrombin-antithrombin complex (TAT), soluble fibrin (SF) and soluble fibrin monomer complex (SFMC) in coagulation systems, and Fibrin degradation product (FDP) and D-dimer in fibrinolytic systems. They are relatively new coagulation biomarkers and the characteristics of them are to be rapidly elevated in acute phase. In clinical situation, they are practically used to detect the venous thromboembolism [4–6]. Besides, FDP and D-dimer are more studied, and the clinical applications of these coagulation biomarkers are ranging from diagnosing [7] to the treatment [8].

In this chapter, we present information on the successful use of FDP, D-dimer and fibrinogen in clinical practice. Finally, we demonstrate the prospects of the clinical application of coagulation biomarkers.

2. Disseminated intravascular coagulation (DIC) and clinical use of coagulation biomarkers

The occurrence of DIC has been the definitive trigger for the use of coagulation biomarkers in the diagnosis of this disease. DIC is characterized by the widespread activation of coagulation, which results in the intravascular formation of fibrin and, ultimately, the thrombotic occlusion of small- and mid-sized vessels [9–11]. Intravascular coagulation can also compromise the blood supply to organs and peripheral cells, and, in conjunction with hemodynamic and metabolic derangements, may contribute to the failure of multiple organs [12].

DIC is present in many clinical conditions (**Table 1**) [12].

Of these clinical conditions, coagulation biomarkers have been especially used in the treatment of sepsis. The clinical criteria for the early diagnosis of DIC have incorporated the use of several coagulation biomarkers such as FDP, D-dimer, PT, and fibrinogen [13–16]. In addition, the two endogenous anticoagulants, antithrombin and protein C, are found decreased in patients with DIC, and are useful in predicting the outcome of such patients, as well as those with sepsis [17, 18]. Furthermore, thrombomodulin, tissue factor pathway inhibitor, Von Willebrand factor and Adamts 13 are also useful in clinical situations [19, 20].

Of these coagulation biomarkers, we focused on the use of FDP and D-dimer in several clinical conditions. D-dimer is a specific protein fiber degradation product of cross-linked fibrin in response to hydrolysis by fibrinolytic enzymes [21, 22]. When the thrombus degrades, D-dimer may be released into the circulatory system [23]. In normal blood, the level of D-dimer is low, but once thrombosis occurs, the D-dimer level rises [24]. FDP is the degradation product of fibrous protein. In normal blood, the level of FDP is also low; however, the FDP level also increases when fibrinolysis occurs. FDP is a mitogen for many cell types, promoting the proliferation of endothelial cells, smooth muscle cells, and fibroblasts, as well

Sepsis

Trauma

    Serious tissue injury

    Head injury

    Fat embolism

Cancer

    Myeloproliferative diseases

    Solid tumors (e.g., pancreatic carcinoma, prostatic carcinoma)

Obstetrical complications

    Amniotic-fluid embolism

    Abruption placentae

Vascular disorders

    Giant hemangioma (Kasabach-Merritt syndrome)

    Aortic aneurysm

Severe hepatic failure

Reactions to toxins (e.g., snake venom, drugs and amphetamines)

Immunologic disorders

    Severe allergic reaction

    Hemolytic transfusion reaction

    Transplant rejection

Table 1. Common clinical conditions associated with disseminated intravascular coagulation.

as cholesterol deposition [25]. FDP can also induce the adhesion and accumulation of white blood cells, which results in damage to the blood vessel endothelium [26].

In our facility, FDP and D-dimer are measured by an immunoturbidimetric method using Cs-2000i and Cs-5100 systems (Sysmex Corporation., Hyogo, Japan; **Figure 1**). It takes about 15–20 minutes to measure FDP and D-dimer with this instrument.
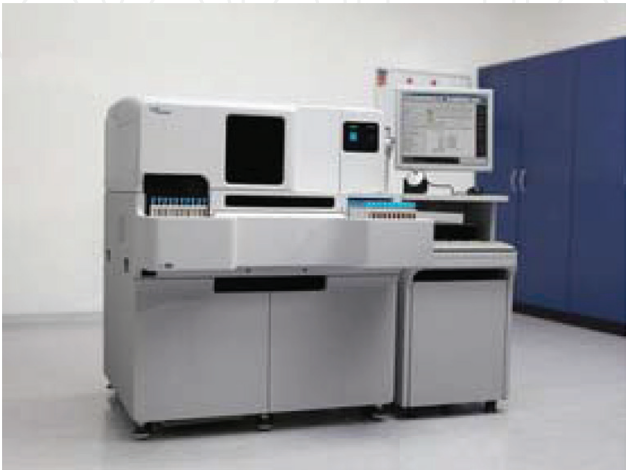

Figure 1. Cs-5100 systems to measure FDP and D-dimer (Sysmex Corporation., Hyogo, Japan).

3. Trauma

DIC has been well known to occur in trauma since the 1960s, especially in relation to head trauma (**Table 1**). Coagulopathy in trauma was believed to originate as a consequence of fluid administration and hypothermia [27]. However, in the 2000s, the concept of acute traumatic coagulopathy (ATC) first appeared [27] with the demonstration that an organ and/or cell injury itself caused the coagulopathy. Using coagulation biomarkers such as PT, APTT and thrombin time (TT), acute traumatic coagulopathy was shown to be associated with mortality and severe trauma.

Initially, the concept of ATC was reported mainly in severe trauma, because PT, APTT and TT were found to have normal values in lightly and mildly traumatized patients. However, using fibrinolytic coagulation biomarkers such as FDP and D-dimer, we also detected ATC in lightly and mildly traumatized patients. This has been described in our first report on the clinical usefulness of coagulation biomarkers [28].

3.1. The relationship between coagulation biomarkers and trauma severity

Our study reported that of all coagulation biomarkers, FDP and D-dimer were associated with the severity of trauma [28]. We have previously demonstrated an association between FDP and D-dimer, and a trauma score such as the Injury Severity Score (ISS) [29]. The ISS has been one of the most common and useful scoring systems to evaluate the severity of trauma and is used widely throughout the world. In clinical practice, the ISS is calculated for each anatomical injury according to the results of physical examinations, surgery and imaging studies; therefore, the ISS cannot be calculated in an initial emergency field. However, we can predict ISS using FDP and D-dimer.

In this study, the area under receiver operating characteristics curves (AUROCs) of FDP and D-dimer for predicting an ISS ≥ 9 were 0.757 and 0.756, and the sensitivity and specificity of FDP and D-dimer based on the Youden's index were 75.9 and 68.4%, and 75.9 and 73.7%, respectively. This demonstrated that we could predict mild to severe injury (ISS ≥ 9) with about 70% sensitivity and specificity; this finding signaled to trauma physicians and surgeons that minor injury was not to be overlooked. Because several minor injuries, such as minute spinal column and rib fractures, are sometimes hard to detect, FDP and D-dimer can be used as supplementary diagnostic tools.

In addition, we have adopted this finding to more severe trauma. In the previous study, we investigated the association between FDP and D-dimer, and an ISS ≥ 9. In a similar setting, we calculated the AUROCs of FDP and D-dimer for predicting ISS ≥ 9, ISS ≥ 16 and ISS ≥ 25 (**Figure 2**).

These figures demonstrated that the predictivity of FDP and D-dimer for ISS was more accurate, especially in severe trauma. In **Table 2**, the AUROC and cut-off points of FDP and D-dimer to predict whether the ISS was over the 25 were the highest at 0.818 and 0.813, respectively. The sensitivities and specificities, based on the Youden's index, of FDP and D-dimer to
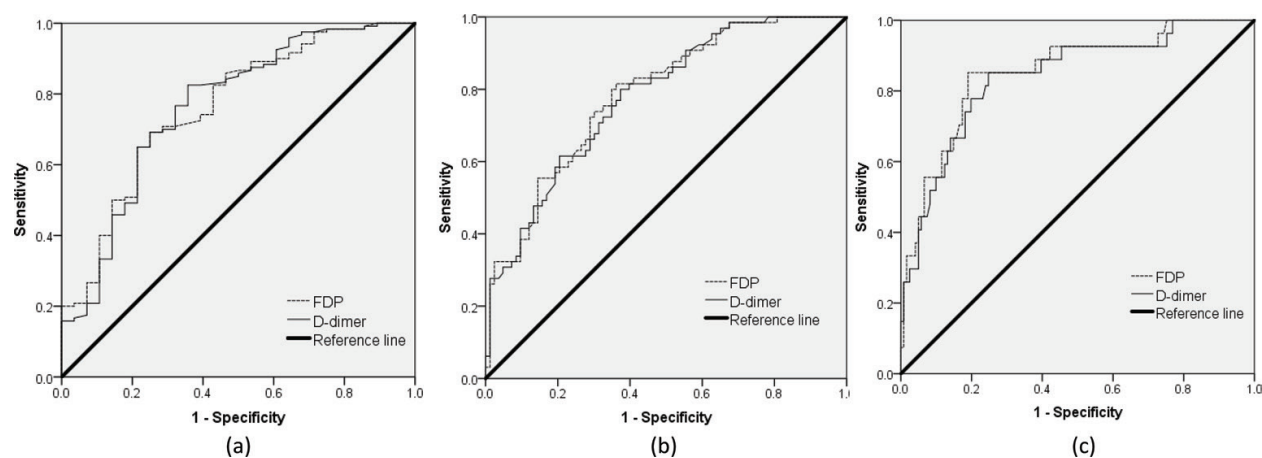
Figure 2. (a) Receiver operating characteristic (ROC) curve of coagulation biomarkers to predict the injury severity score (ISS) of a patient with trauma ≥9 points. FDP, fibrin degradation products. (b) Receiver operating characteristic (ROC) curve of coagulation biomarkers to predict the injury severity score (ISS) of a patient with trauma ≥16 points. FDP, fibrin degradation products. (c) Receiver operating characteristic (ROC) curve of coagulation biomarkers to predict the injury severity score (ISS) of a patient with trauma ≥25 points. FDP, fibrin degradation products.

FDP D-dimer	ISS ≥ 9	ISS ≥ 16	ISS ≥ 25
AUROC (95% CI)	0.743 (0.681–0.806)	0.691 (0.624–0.759)	0.818 (0.735–0.901)
	0.751 (0.689–0.814)	0.694 (0.628–0.761)	0.813 (0.732–0.894)
Cut-off point	32.1 μg/mL	32.1 μg/mL	101.4 μg/mL
	6.5 μg/mL	12.8 μg/mL	28.2 μg/mL
Sensitivity, %	59.4	67.8	73.3
	73.1	65.6	76.7
Specificity, %	79.8	64.9	82.7
	66.7	66.1	78.4

CI, confidence interval; FDP, fibrin degradation product; AUROC, area under the receiver operating characteristic curve; ISS, injury severity score.

Table 2. Area under the receiver operating characteristic curve and cut-off points of FDP and D-dimer to predict whether the ISS is over 9, 16 or 25.

predict an ISS over 25 were 73.3 and 82.7%, and 76.7 and 78.4%, respectively. These findings are novel because they are based on a patient's trauma severity, allowing the development of definitive treatment more rapidly.

3.2. The prediction of extravasation in pelvic fracture using coagulation biomarkers

In the section of the relationship between coagulation biomarkers and trauma severity the ability of FDP and D-dimer to predict trauma severity was demonstrated. Therefore, we also applied this to pelvic fracture [30]. Pelvic fracture is an independent risk factor for death after blunt trauma. It is associated with increased mortality in blunt trauma, with rates up to 30%

[31–33]. In pelvic fracture, retroperitoneal hemorrhage may induce hemodynamic instability, with 5–20% originating from arterial bleeding [34].

In a clinical situation, the standard tool to detect arterial bleeding in a pelvic fracture has been computed tomography (CT) using contrast material; however, several problems exist with CT scanning. One problem is the specificity of CT scanning to detect arterial bleeding in pelvic fracture [35] is decreased. Another problem is that the quality of the CT scanning may be related to the scanning protocol and can be affected by interference caused by vasospasm, consequently affecting the diagnostic ability of physicians [36, 37]. Thus, we evaluated the predictive ability of coagulation biomarkers to detect arterial bleeding and whether these could be used as alternative tools for CT scanning.

Our report highlighted the highly accurate ability of FDP and D-dimer to detect arterial bleeding in a pelvic fracture; the AUROCs of FDP and D-dimer were 0.900 and 0.882, respectively (**Table 3**) [30]. In addition, in this study we calculated the ratios of FDP to fibrinogen, and of D-dimer to fibrinogen. Fibrinogen is said to be an independent risk factor of mortality and severity in blunt trauma patients [38–40], and a predictor of transfusion [41, 42]. We combined the high FDP and D-dimer, and the low fibrinogen, to the ratio of FDP to fibrinogen and the ratio of D-dimer to fibrinogen, this was a novel finding. This ratio was subsequently developed to the next stage [43, 44].

3.3. Prediction of the need for packed red blood cell transfusions using coagulation biomarkers

We applied coagulation biomarkers to the prediction of the need for packed red blood cell transfusions [43]. For a long time, many investigators have discussed how to predict massive transfusion requirements in blunt trauma patients [45–51]. The characteristics of FDP and D-dimer were correlated with the trauma severity: from relatively light to severe trauma [28]. This feature has been utilized to predict not only patients requiring massive transfusions, but also whether patients needed packed red blood cells or not. Coagulation biomarkers,

	FDP	D-dimer	Ratio of FDP to fibrinogen	Ratio of D-dimer to fibrinogen	Hemoglobin level	Lactate level
AUROC	0.900	0.882	0.918	0.900	0.815	0.765
(95% CI)	(0.765–1.000)	(0.728–1.000)	(0.797–1.000)	(0.773–1.000)	(0.656–0.974)	(0.563–0.967)
Cut-off point	126.8 μg/mL	46.0 μg/mL	0.656	0.215	11.0 g/dL	2.75 mmol/L
Sensitivity, %	94.1	94.1	94.1	94.1	61.1	58.8
Specificity, %	90.0	90.0	90.0	80.0	0.0	85.7

CI, confidence interval; FDP, fibrin degradation product; AUROC, area under the receiver operating characteristic curve.

Table 3. Area under the receiver operating characteristic curves and cut-off points of parameters to predict arterial extravasation in pelvic fracture patients.

	AUROC (95% CI)	Cut-off point	Sensitivity (%)	Specificity (%)
ABC	0.591 (0.420–0.763)	0.5	21.4	96.7
GCS	0.716 (0.547–0.885)	12.5	96.4	42.9
Ht	0.667 (0.503–0.830)	31.3%	97.3	35.7
PT–INR	0.859 (0.760–0.958)	1.065	71.4	90.1
APTT	0.684 (0.501–0.866)	36.45 s	42.9	96.4
Fib	0.877 (0.808–0.947)	245.5 mg/dL	64.3	100
FDP	0.874 (0.784–0.963)	45.65 μg/dL	78.6	80.4
FDP/Fib ratio	0.899 (0.819–0.979)	0.202×10^{-3}	85.7	82.3

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; ABC, assessment of blood consumption score; GCS, Glasgow Coma Scale; Ht, hematocrit; PT-INR, international normalized ratio of prothrombin time; APTT, activated partial thromboplastin time; Fib, fibrinogen; FDP, fibrin degradation product.

Table 4. Results of receiver operating characteristic curves analysis.

especially, the ratio of FDP to fibrinogen, were found to be the most accurate markers for predicting the need for packed red blood cell transfusions (**Table 4**) [43].

4. Cardiac pulmonary arrest

In recent decades, the science of cardiac pulmonary arrest (CPA) has been improving due to the widespread adoption of guidelines by the International Liaison Committee on Resuscitation (ILCOR). The 2015 guidelines by the Japan Resuscitation Council, which is one of the subsidiary organizations of ILCOR, enumerates predictive candidates for outcomes of patients with an out-of-hospital cardiac arrest (OHCA), such as S-100B, neuron specific enolase, imaging findings, brain waves, among others. However, it is presently difficult to predict favorable neurological outcomes or the survival of patients with OHCA [52]. Recently, several reports have suggested that blood coagulation makers reflected the prognosis of patients with CPA. The occurrence of fibrinolysis in patients with CPA has been noticed for a long time [53]; however, coagulation biomarkers has not been clinically applied to CPA until recently, with clinical applications with

	AG	ACAG	FDP	D-dimer
AUROC (95% CI)	0.664 (0.514–0.815)	0.667 (0.516–0.818)	0.714 (0.571–0.858)	0.707 (0.561–0.853)
Cut-off point	27.8 mmol/L	31.7 mmol/L	29.4 μg/mL	10.2 μg/mL
Sensitivity, %	84.4	78.1	87.5	87.5
Specificity, %	45.0	55.0	50.0	55.0

AG, anion gap; ACAG, albumin-corrected anion gap; CI; confidence interval; FDP, fibrin degradation products; AUROC, areas under receiver operating characteristic curves.

Table 5. Areas under receiver operating characteristic curves and cut-off points of parameters that predict whether a patient with cardiopulmonary arrest can achieve a return of spontaneous circulation after effective cardiopulmonary resuscitation.

regard to CPA having appeared since the 2010s. For example, FDP and D-dimer are associated with the return of spontaneous circulation (ROSC) and have been useful for predicting ROSC [54] (**Table 5**) [54]. Other reports have demonstrated that a high D-dimer concentration on admission predicts a poorer outcome [55], and that the FDP level predicts neurological outcomes [56].

5. Conclusion

Coagulation disorders are associated with several diseases and symptoms in emergency medical fields. The occurrence of DIC is a modern topic and has been accelerating the studies about the coagulation biomarkers. We demonstrated that testing for and measuring FDP and/or DD may be advantageous in diagnosing and/or treatment of trauma and CPA.

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Conflict of interest

The authors declare that they have no competing interests.

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