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D-dimer kit with a High FDP/D-Dimer Ratio is Useful for Diagnosing Thrombotic Diseases

Nozomi Ikeda[1], Hideo Wada[2], Yuhuko Ichikawa[1], Minoru Ezaki[1], Motoko Tanaka[1], Shinya Hiromori[1], Katsuya Shiraki[2], Isao Moritani[3], Akitaka Yamamoto[4], Hideto Shimpo[5], and Motomu Shimaoka[6]

Abstract

Introduction: Although D-dimer is a useful biomarker of thrombosis, there are many D-dimer kits, with high and low fibrinogen and fibrin degradation products (FDP)/ D-dimer ratios.

Methods: Plasma D-dimer levels were measured using three different kits in critically ill patients to examine the usefulness of such measurements for detecting the thrombotic diseases and determining the correlation with the FDP and FDP/D-dimer ratio.

Results: Although three D-dimer kits showed marked utility for diagnosing disseminated intravascular coagulation (DIC) and peripheral arterial and venous thromboembolism (PAVTE), the D-dimer levels determined using the three kits varied among diseases. Indeed, one D-dimer kit showed a high FDP/D-dimer ratio, and another kit showed a low FDP/D-dimer ratio. D-dimer kit with low FDP/D-dimer ratio tended to have high cut-off values and low specificity for diagnosing DIC and PAVTE. In D-dimer kit with high FDP/D-dimer ratio, FDP/D-dimer ratios in patients with thrombosis was significantly higher than that in patients without thrombosis.

Conclusion: All three D-dimer kits show utility for detecting thrombotic diseases. However, the D-dimer levels determined using the kits varied due to differences in the FDP/D-dimer ratio. In combination with the FDP level, a D-dimer kit with a high FDP/D-dimer ratio may be useful.

Keywords

D-dimer, FDP, thrombosis, DIC

Introduction

D-dimer is the most frequent used fibrin-related marker (FRM)[1] including fibrinogen and fibrin degradation products (FDPs) as well as soluble fibrin (SF) and SF monomer complex (SFMC), and is used as a negative or positive predictive biomarker for venous thromboembolism (VTE)[2,3] and as a diagnosing biomarker for disseminated intravascular coagulation (DIC).[4,5] Elevated D-dimer levels reportedly predict the onset of deep vein thrombosis (DVT) after total hip arthroplasty or total knee arthroplasty;[6] however, the administration of anticoagulation[7–9] cancels the utility in predicting postoperative DVT. In addition, elevated D-dimer levels have been reported to suggest massive bleeding in patients undergoing major operations.[9] Although D-dimer levels can be used to both diagnose or rule out VTE,[10,11] adequate cut-off values for predicting thrombosis have not been established. The FDP/D-dimer ratio was reported to be significantly high in patients with DIC[12] and non-survivor.[13] As various D-dimer kits are now available, the FDP/D-dimer ratio might vary among various kits.

D-dimer elevation may be associated with a high risk of a poor prognosis in patients with coronavirus disease 2019 (COVID-19) due to thrombosis.[14–16] Elevated D-dimer levels have also been reported to be a high-risk factor in

[1] Mie Prefectural General Medical Center, Yokkaichi, Japan
[2] Mie Prefectural General Medical Center, Yokkaichi, Japan
[3] Mie Prefectural General Medical Center, Yokkaichi, Japan
[4] Mie Prefectural General Medical Center, Yokkaichi, Japan
[5] Mie Prefectural General Medical Center, Yokkaichi, Japan
[6] Mie University Graduate School of Medicine, Tsu, Japan

Corresponding Author:
Hideo Wada, Department of General and Laboratory Medicine, Mie Prefectural General Medical Center, Associated Department with Mie Graduate School of Medicine, 5450–132 Ohaza Hinaga, Yokkaichi, Mie 510–8561 Japan.
Email: wadahide@clin.medic.mie-u.ac.jp

critically ill patients without COVID-19, including infectious disease, trauma, heart failure, thrombotic disease (eg cerebral thrombosis, acute myocardial infarction, VTE), intracranial bleeding, and other conditions.[17] However, there are many kits available for assaying D-dimer levels, and the standardization of D-dimer elevation for diagnosing of thrombosis is still required.

In this study, three different D-dimer and FDP levels were examined in critically ill patients with various diseases and the relationship between D-dimer levels, FDPs and the FDP/D-dimer ratio in critically ill patients was investigated.

Material and Methods

The study population included patients with the following conditions who were managed at Mie Prefectural General Medical Center; unidentified clinical syndrome, (UCS; $n = 98$), infectious disease ($n = 184$), acute cerebral infarction (ACI; $n = 130$) hematological malignancy ($n = 23$), acute coronary syndrome (ACS; $n = 40$) solid cancer ($n = 68$), peripheral arterial and venous thromboembolism (PAVTE; $n = 34$) and DIC ($n = 81$). DIC was diagnosed using the Japanese Ministry of Health Labor and Welfare criteria for DIC.[18] ACI was diagnosed using computed tomography or magnetic resonance imaging, ACS was diagnosed using coronary angiography, electrocardiogram and elevated troponin levels, VTE was diagnosed using computed tomography or venous ultrasound. Patients with UCLS had some symptom, but they were diagnosed as having no underlying diseases or thrombosis based on imaging findings. Patients without thrombosis had no symptomatic thrombosis.

D-dimer A was measured using LIASAUTO D-dimer Neo (Sysmex, Kobe, Japan) with an automatic coagulation analyzer (CS-5100; Sysmex). D-dimers B and C were measured using LPIA-ACE D-Dimer II (LSI Medience, Tokyo, Japan) and LPIA-Genesis (LSI Medience), respectively, with the STACIA system (LSI Medience). SF and FDPs were measured using Iatro SF II (LSI Medience) and LPIA FDP-P (LSI Medience), respectively, with the STACIA system (LSI Medience). The intra- and inter- assay coefficient of variation were ≤3.0% in all D-dimer assays.

The study protocol (2019-K9) was approved by the Human Ethics Review Committee of Mie Prefectural General Medical Center, and informed consent was obtained from each participant. This study was carried out in accordance with the principles of the Declaration of Helsinki.

Statistical Analyses

The data are expressed as the median (25th-75th percentiles). The significance of differences between groups was examined using the Mann-Whitney U-test. The cut-off values were examined by a receiver operating characteristic (ROC) analysis.

P values of <0.05 were considered to indicate a statistically significant difference. All of the statistical analyses were performed using the Stat-Flex software program (version 6; Artec Co Ltd, Osaka, Japan).

Table 1. Plasma levels of FDP, D-dimer, and SF in patients with various diseases

Group Disease	(1) DIC	(2) PAVTE	(3) ACI	(4) ACS	(5) Solid Cancer	(6) HM	(7) Infection	(8) UCS
FDP (μg/ml)	60.7 (27.2–189)	12.2 (4.8–22.8)	1,7 (1.0–3.1)	2.4 (1.1–9.2)	4.1 (2.1–17.1)	2.2 (1.5–9.0)	3.6 (1.4–10.7)	0.8 (0.6–1.1)
P compared with group	2, 3, 4, 5, 6, 7, 8, ***	1, 3, 4, 7, 8, ***; 5, 6, **	1, 2, 5, 7, 8, ***; 6 *	1, 2, 6, 8, ***; 5, *	1, 3, 8 ***; 2, **; 4, *	1, 8, ***; 2, **; 3, *	1, 2, 3, 8, ***	1, 2, 3, 4, 5, 6, 7, ***
D-dimer A (μg/ml)	44.8 (26.5–74.2)	11.1 (4.5–18.9)	1.2 (0.5–2.4)	1.6 (0.7–9.5)	4.2 (1.4–13.5)	2.2 (1.0–9.9)	3.3 (1.0–8.6)	0.5 (0.5–0.5)
P compared with group	2, 3, 4, 5, 6, 7, 8, ***	1, 3, 4, 7, 8, ***; 5, 6, **	1, 2, 5, 7, 8, ***; 6, *	1, 2, 8, ***; 5, *	1, 3, 8 ***; 2, **; 4, *	1, 8, ***; 2, **; 3, *	1, 2, 3, 8, ***	1, 2, 3, 4, 5, 6, 7, ***
D-dimer B (μg/ml)	30.0 (19.4–45.8)	9.8 (4.1–15.5)	1.2 (0.7–2.4)	1.9 (0.8–8.0)	3.6 (1.3–11.0)	1.7 (1.1–9.2)	2.9 (0.9–8.1)	0.5 (0.4–0.7)
P compared with group	2, 3, 4, 5, 6, 7, 8, ***	1, 3, 4, 6, 8, ***; 7, **	1, 2, 5, 7, 8, ***;	1, 2, 8, ***; 5, *	1, 3, 8 ***; 4, 6, *	1, 2, ***; 8, **; 5, 7, *	1, 3, 8, ***; 2. **; 6, *	1, 2, 3, 4, 5, 7, ***; 6, **
D-dimer C (μg/ml)	23.7 (15.6–44.1)	9.0 (4.4–15.5)	1.2 (0.6–2.4)	1.4 (0.7–7.9)	3.2 (1.5–10.0)	1.9 (1.1–8.2)	2.9 (1.0–7.9)	0.5 (0.3–0.7)
P compared with group	2, 3, 4, 5, 6, 7, 8, ***	1, 3, 4, 7, 8, ***; 5, 6, **	1, 2, 5, 7, 8, ***; 6, *	1, 2, 8, ***; 5, *	1, 3, 8 ***; 2, **; 4, *	1, 8, ***; 2, **; 3, *	1, 2, 3, 8, ***	1, 2, 3, 4, 5, 6, 7, ***
SF (μg/ml)	58.1 (28.0–124)	19.5 (12.2–50.9)	7.1 (2.7–11.8)	8.2 (4.1–18.3)	12.8 (6.6–39.4)	8.9 (3.9–12.1)	12.3 (6.3–24.3)	3.0 (1.5–7.6)
P compared with group	2, 3, 4, 5, 6, 7, 8, ***	1, 3, 4, 7, 8, ***; 5, 6, **	1, 2, 5, 7, 8, ***; 6, *	1, 2, 8, ***;	1, 3, 8 ***; 2, **	1, 8, ***; 2, **; 3, *	1, 2, 3, 8, ***	1, 2, 3, 4, 5, 6, 7, ***

Data are shown as the median (25–75 percentile). DIC, disseminated intravascular coagulation; PAVTE, peripheral arterial and venous thromboembolism, ACI, acute cerebral infarction; ACS, acute coronary syndrome; HM, hematological malignancy; UCS, unidentified clinical syndrome; FDP, fibrinogen and fibrin degradation product; D-dimer A, LIASAUTO D-dimer Neo, D-dimer B, LPIA-ACE D-Dimer II, D-dimer C, LPIA-Genesis; SF, soluble fibrin; ***, $p<0.001$; **, $p<0.01$; *, $p<0.05$

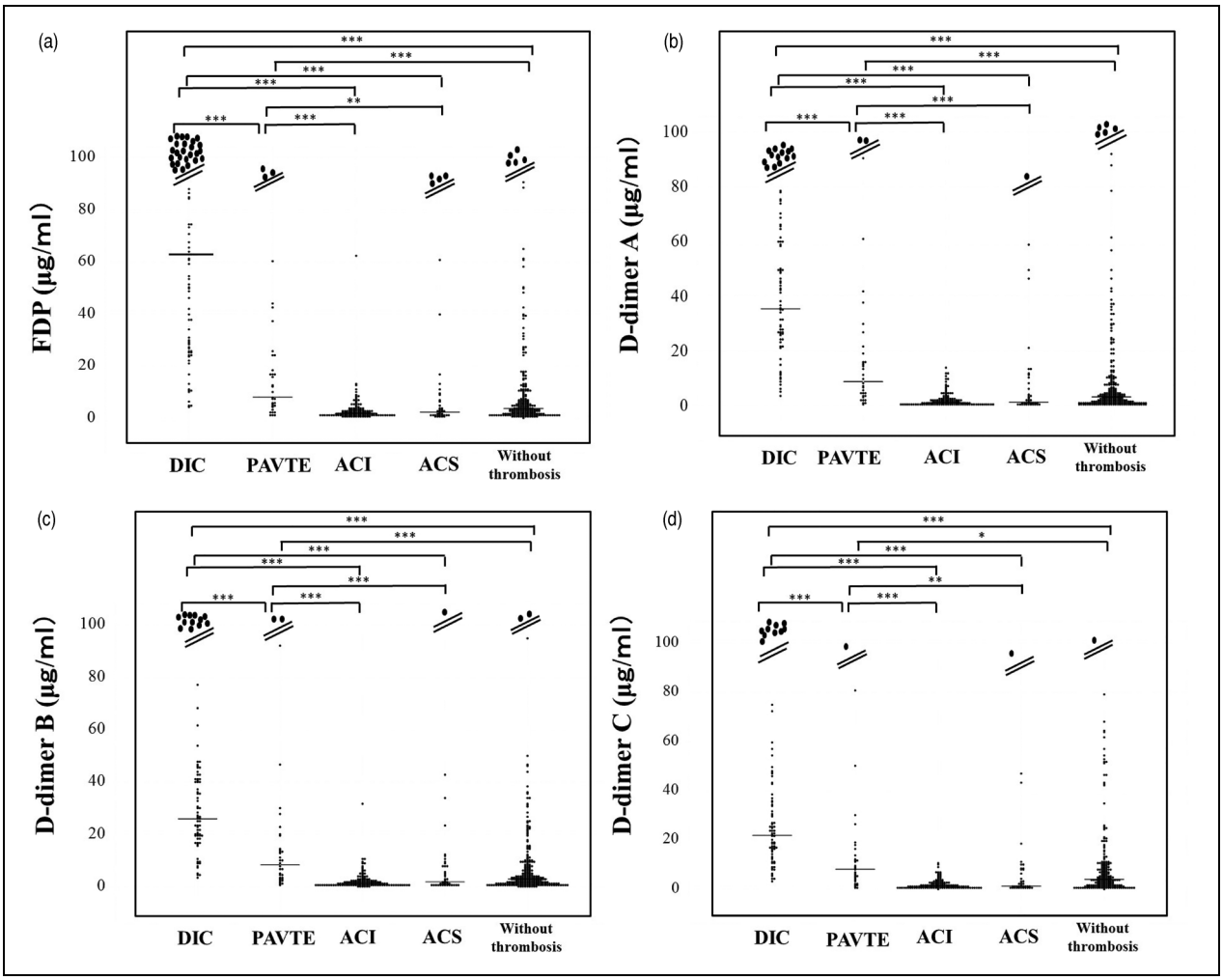

Figure 1. Plasma levels of FDP (a) and D-dimer A (b), B(c) and C(d) DIC, disseminated intravascular coagulation; PAVTE, peripheral arterial and venous thromboembolism, ACI, acute cerebral infarction; ACS, acute coronary syndrome; FDP, fibrinogen and fibrin degradation product; D-dimer A, LIASAUTO D-dimer Neo, D-dimer B, LPIA-ACE D-Dimer II, D-dimer C, LPIA-Genesis; SF, soluble fibrin; Plasma FDP or D-dimer levels ≤80μg/ml were plotted. ***, $p<0.001$; **, $p<0.01$; *, $p<0.05$

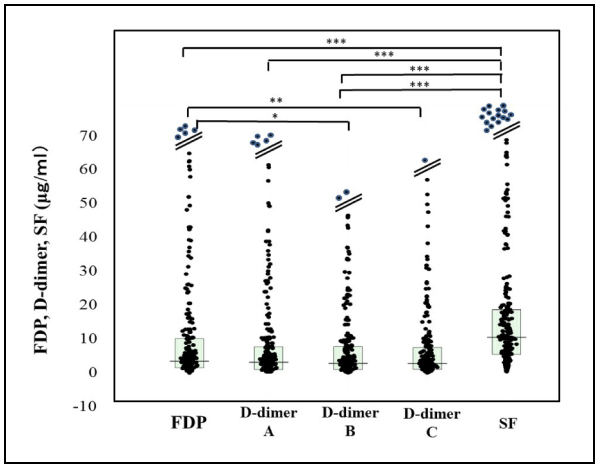

Figure 2. Plasma levels of FDP, D-dimer A, B and C in patients without thrombosis FDP, fibrinogen and fibrin degradation product; D-dimer A, LIASAUTO D-dimer Neo, D-dimer B, LPIA-ACE D-Dimer II, D-dimer C, LPIA-Genesis; SF, soluble fibrin; ***, $p<0.001$; **, $p<0.01$; *, $p<0.05$

Results

The plasma FDP, SF and D-dimer A-C levels in patients with DIC or PAVTE were significantly higher than those in patients with other conditions. These FRMs were also significantly higher in patients with ACI, ACS, solid cancer, hematological malignancy and infection than in those with UCS. The median D-dimer A level was significantly higher than that of D-dimer B which was significantly higher than that of D-dimer C in patients with DIC (Table 1). The plasma FDP and D-dimer A-C levels in patients with DIC or PAVTE were significantly higher than those in patients without thrombosis, but those in patients with ACI or ACS were not significantly higher than those in patients without thrombosis (Figure 1). In the analysis of patients without thrombosis, the levels of FDP D-dimer A-C and SF were markedly high. The plasma FDP levels were significantly different from D-those of D-dimer B and C as well as SF but were not markedly different from those of D-dimer A (Figure 2).

Table 2. Results of an ROC analysis of fibrin related markers for DIC score ≥6 versus DIC score ≤4

	AUC	Cut-off value-1 (μg/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	Odds ratio	Cut-off value -2 (μg/ml)	Sensitivity (%)	Specificity (%)
FDP	0.928	18.5	87.4	87.4	72.4	49.2	3.8	100	52.3
D-dimer A	0.929	16.9	85.8	85.8	68.0	38.6	3.7	100	55.4
D-dimer B	0.919	15.4	86.4	86.4	69.3	41.2	3.2	100	53.2
D-dimer C	0.859	12.1	81.3	81.3	61.9	19.1	3.2	100	42.1
SF	0.655	41.1	63.4	63.4	40.8	3.01	3.9	100	12.2

Cut-off value −1 represents the cross point between the sensitivity and specificity curves. Cut-off value-2 is the highest value in negative predictive value 100%. ROC, receiver operating characteristics; AUC, area under the curve; PPV, positive predictive value; FDP, fibrinogen and fibrin degradation product; D-dimer A, LIASAUTO D-dimer Neo, D-dimer B, LPIA-ACE D-Dimer II, D-dimer C, LPIA-Genesis; SF, soluble fibrin

According to an ROC analysis for DIC (DIC score ≥6 vs ≤4), the area under the curve (AUC) was ≥9.000 for FDPs and D-dimer A and B (Table 2). The cut-off value-1 for the cross point between the sensitivity and specificity curves was 16.9 μg/ml for D-dimer A, 15.4 μg/ml for D-dimer B and 12.1 μg/ml for D-dimer C. The cut-off value-2, which is the highest value at which the sensitivity is 100%, was 3.7 μg/ml for D-dimer A and 3.2 μg/ml for D-dimers B and C. Regarding the ROC analysis for PAVTE (PAVTE vs UCS), the AUC was ≥0.977 for FDPs and D-dimers A-C (Table 3). Regarding the ROC analysis for patients with PAVTE or DIC versus patients without thrombosis, the AUC was similar among FDP and D-dimer A-C and the cut-off value according to the ROC analysis was 10.0 μg/ml for D-dimer A, 9.0 μg/ml for D-dimer B and 8.3 μg/ml for D-dimer C (Table 4). At cut-off values of 7.8 μg/ml or 3.2 μg/ml, the sensitivity of D-dimer A tended to be high but the specificity low compared to those of D-dimer C.

Regarding the correlation with FDP, the R-value was 0.768 for D-dimer A, 0.764 for D-dimer B and 0.686 for D-dimer C, and the slope was 0.992 for D-dimer A, 1.440 for D-dimer B, and 1.892 for D-dimer C (Figure 3). Regarding the correlation among D-dimers A, B and C, the R-values was ≥0.900 for D-dimer A and B, and D-dimer A and C but 0.886 for D-dimer B and C (Figure 4).

The FDP/D-dimer ratio was the highest for D-dimer C and lowest for D-dimer A, and the ratio using D-dimer B and C varied among various diseases (Table 5). The FDP/D-dimer levels were significantly lower in patients with PAVTE, ACI, ACS, solid cancer or infection than in patients with UCS or DIC. In our analysis of FDP/D-dimer ratio using D-dimer C, FDP/D-dimer ratio in patients with DIC, or PAVTE was significantly higher than that in patients without thrombosis (Figure 5).

Discussion

The median values of plasma D-dimer value in patients with UCS was 0.5 μg/ml for all three D-dimer kits, suggesting that the patients with a D-dimer value ≤0.5 μg/ml may not be complicated with thrombotic disorders. However, the plasma D-dimer levels increased in patients with thrombotic diseases, such as DIC, PAVTE, ACI and ACS, and underlying diseases of thrombosis, such as solid cancers, infection and hematological malignancy. The plasma D-dimer levels in the patients with DIC and those with PAVTE were extremely high, resulting in a high AUC in the ROC analysis.

The DIC score in several diagnostic systems[4,5] showed the strongest relationship with a poor outcome, followed by FRMs including the D-dimer level. However, D-dimer elevation was not included in the scoring system to diagnose sepsis-induced coagulopathy.[19,20] This was because there are many D-dimer kits, and many different D-dimer kits have different cut-off value.[16] Many studies have been performed using very low cut-off values such as 0.5 to 0.8 μg/ml.[21–23] Our findings showed that the D-dimer cut-off value that excluded DIC was 3.2 μg/ml, suggesting that the cut-off value of the ISTH overt-DIC scoring system should be ≥3.2μg/ml.

Table 3. Results of an ROC analysis of fibrin-related markers for PAVTE (PAVTE versus UCS)

VTE	AUC	Cut-off value −1 (μg/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	Odds ratio	Cut-off value −2 (μg/ml)	Sensitivity (%)	Specificity (%)
FDP	0.993	2.0	95.9	95.9	91,1	482	1.2	100	79.6
D-dimer c	0.999	1.1	97.8	97.8	95.5	2016	1.0	100	96.0
D-dimer B	0.997	1.5	97.7	97.7	97.7	4074	1.0	100	87.8
D-dimer C	0.977	1.2	97.7	97.7	97.7	4074	0.8	100	86.8
SF	0.887	8.8	80.6	80.6	64.8	18.2	1.1	100	19.4

Cut-off value −1 represents the cross point between the sensitivity and specificity curves. Cut-off value-2 is the highest value in negative predictive value 100%. ROC, receiver operating characteristics; AUC, area under the curve; PPV, positive predictive value; FDP, fibrinogen and fibrin degradation product; D-dimer A, LIASAUTO D-dimer Neo, D-dimer B, LPIA-ACE D-Dimer II, D-dimer C, LPIA-Genesis; SF, soluble fibrin

Table 4. Results of an ROC analysis of fibrin related markers for DIC and PAVTE (DIC and PAVTE vs without thrombotic diseases)

	AUC	Cut-off value (ROC)	Sensitivity (%)	Specificity (%)	Cut-off value −1	Sensitivity (%)	Specificity (%)	Cut-off value −2	Sensitivity (%)	Specificity (%)
FDP	0.850	11.1 μg/ml	77.4	77.3	7.8 μg/ml	83.1	70.8	3.2 μg/ml	96.0	45.4
D-dimer A	0.855	10.0 μg/ml	78.3	77.6	7.8 μg/ml	83.0	73.4	3.2 μg/ml	96.0	46.8
D-dimer B	0.848	9.0 μg/ml	77.4	77.3	7.8 μg/ml	81.5	74.2	3.2 μg/ml	94.4	51.9
D-dimer C	0.843	8.3 μg/ml	77.7	77.3	7.8 μg/ml	79.0	75.1	3.2 μg/ml	94.4	52.4

Cut-off value (ROC) represents the cross point between the sensitivity and specificity curves. Cutoff value-1 and 2 are previously reported.[3]
ROC, receiver operating characteristics; AUC, area under the curve; FDP, fibrinogen and fibrin degradation product; D-dimer A, LIASAUTO D-dimer Neo, D-dimer B, LPIA-ACE D-Dimer II, D-dimer C, LPIA-Genesis; SF, soluble fibrin

The plasma levels of D-dimer were slightly high in patients with ACI, especially cardiogenic ACI[24] and those with ACS, but they were also high in patients with solid cancer, infection, or hematological malignancy. Elevated D-dimer levels were further reported in DIC,[3,4] VTE,[2,3] infection,[17,25] solid cancer[26] and hematological malignancy.[25] The AUC was high in an ROC analysis of DIC and PAVTE, while it was low for ACI and ACS. These findings suggest that complication with DIC or PAVTE may be suggested by elevated D-dimer levels in patients with infection, solid cancer or hematological malignancy, whereas complication with ACI or ACS is unlikely.

The plasma D-dimer levels determined using three D-dimer kits varied among diseases, and the correlation with the FDPs and FDP/D-dimer ratio also differed among the D-dimer kits. It is helpful for physicians to know in advance the normal range, cutoff values for thrombosis and name of the D-dimer kit used in their own hospital. The FDP/D-dimer ratio may

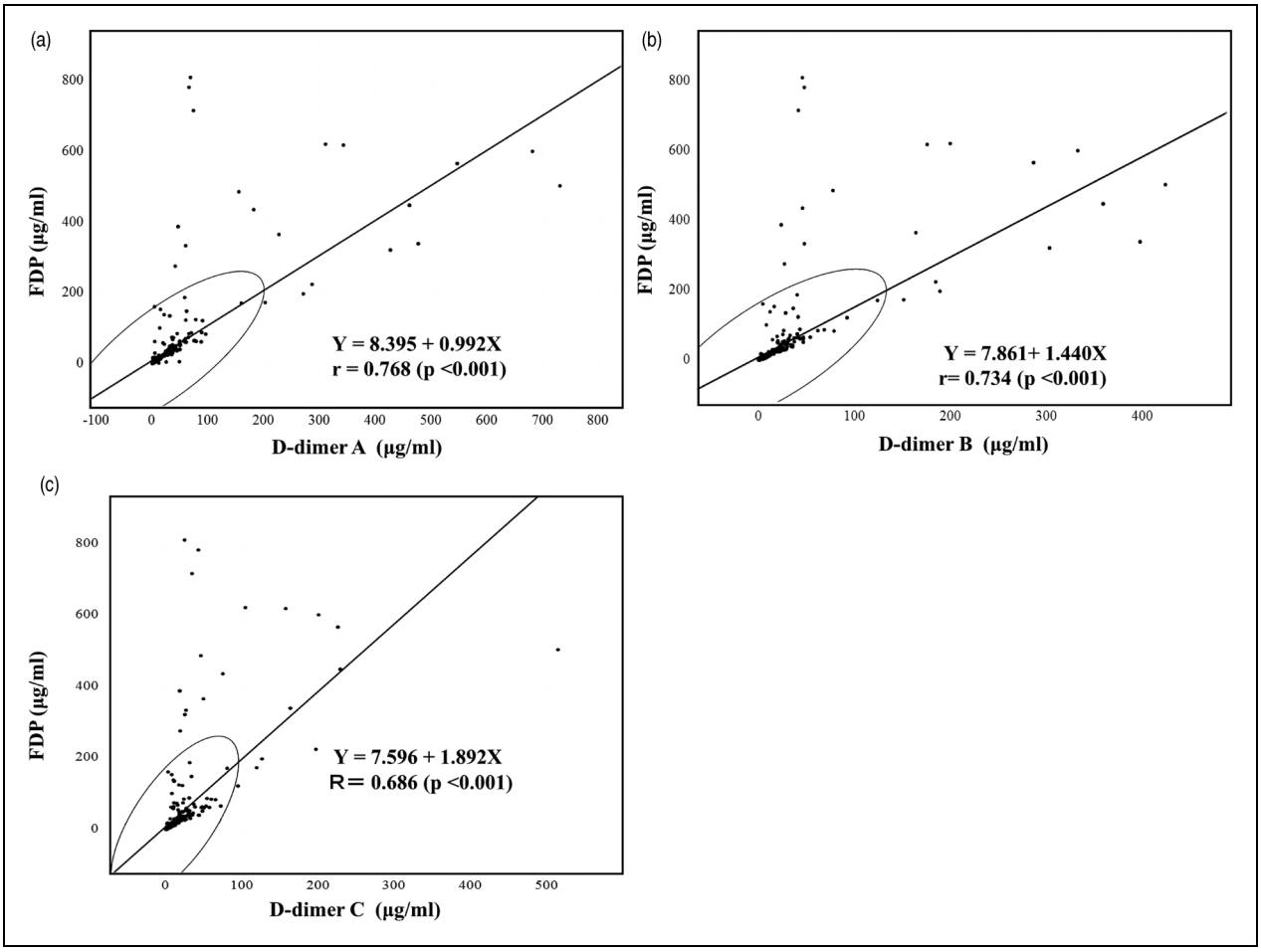

Figure 3. Relationship between FDP and D-dimer A (a), or D-dimer B (b), or D-dimer C. FDP, fibrinogen and fibrin degradation products; D-dimer A, LIASAUTO D-dimer Neo; D-dimer B. LPIA-ACE D-Dimer II; D-dimer C, LPIA-Genesis

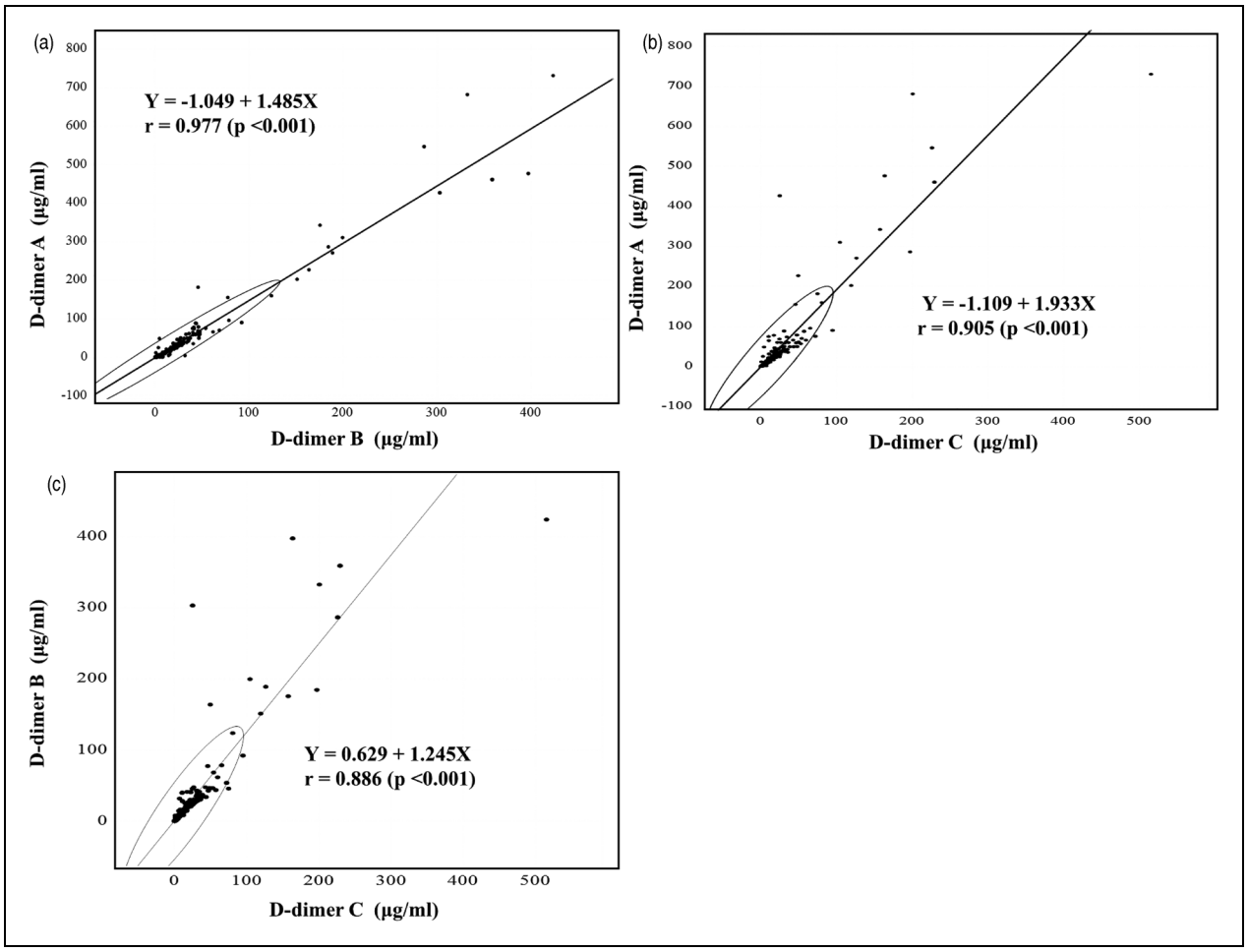

Figure 4. Relationship between D-dimer A and D-dimer B (a), D-dimer A and D-dimer B (b), and D-dimer B and D-dimer C FDP, fibrinogen and fibrin degradation products; D-dimer A, LIASAUTO D-dimer Neo; D-dimer B. LPIA-ACE D-Dimer II; D-dimer C, LPIA-Genesis

depend on fibrinolysis.[12] As the FDP/D-dimer ratio was lower in cases with PAVTE, ACI, ACS, solid cancer and hematological malignancy than in those with UCS or DIC, patients with the above diseases (except for UCS and DIC) might be in a hypofibrinolytic state, resulting in a thrombotic tendency. Although ROC analyses for DIC and PAVTE versus without thrombosis showed a similar AUC, sensitivity and specificity among the three D dimer kits, the adequate cut-off value was higher for the D-dimer kit with a low FDP/D-dimer ratio than for that with a high FDP/D-dimer ratio, and the specificity for

Table 5. FDP/D-dimer ratio in patients with various thrombotic diseases.

FDP/D-dimer ratio	DIC	PAVTE	ACI	ACS	Solid cancer	HM	Infection	UCS
D-dimer A	1.14 (0.97–1.81) $^{\&}$	1.07 (1.00–1.17) $^{\&\&\&}$	1.24 (1.05–1.64)	1.24 (1.06–1.53)	1.12 (0.99–1.31) $^{\&\&\&}$	1.11 (0.96–1.29) $^{\&\&}$	1.16 (1.00–1.44) $^{\&\&\&}$	1.40 (1.18–1.74)
D-dimer B	1.53*** (1.23–2.61)	1.26*** (1.14–1.33) $^{\&\&\&}$	1.28 (1.15–1.57) $^{\&\&\&}$	1.24 (1.10–1.54) $^{\&\&}$	1.29*** (1.16–1.48) $^{\&\&\&}$	1.25 (1.07–1.38) $^{\&\&\&}$	1.29*** (1.12–1.60) $^{\&\&\&}$	1.56* (1.26–2.07)
D-dimer C	1.87*** (1.30–4.33)	1.28*** (1.16–1.45) $^{\&\&\&}$	1.38* (1.21–1.67) $^{\&\&\&}$	1.36* (1.18–1.82) $^{\&\&}$	1.30*** (1.18–1.63) $^{\&\&\&}$	1.19* (1.07–1.57) $^{\&\&\&}$	1.30*** (1.12–1.67) $^{\&\&\&}$	1.65*** (1.35–2.10)

***, $p < 0.001$; *, $p < 0.05$ in comparison with D-dimer A; $^{\&\&\&}$, $p < 0.001$; $^{\&\&}$, $p < 0.01$; $^{\&}$, $p < 0.05$ in comparison with UCS; Data are shown as the median (25–75 percentile). DIC, disseminated intravascular coagulation; PAVTE, peripheral arterial and venous thromboembolism, ACI, acute cerebral infarction; ACS, acute coronary syndrome; HM, hematological malignancy; UCS, unidentified clinical syndrome; FDP, fibrinogen and fibrin degradation product; D-dimer A, LIASAUTO D-dimer Neo, D-dimer B, LPIA-ACE D-Dimer II, D-dimer C, LPIA-Genesis;

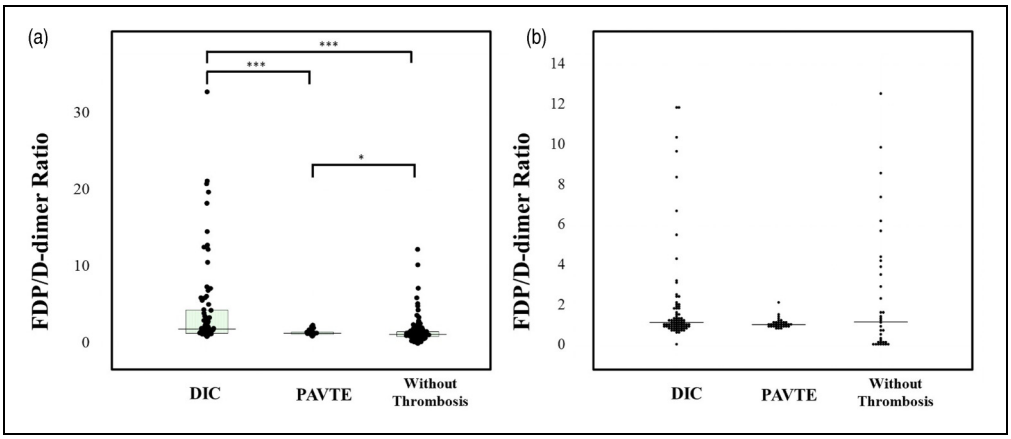

Figure 5. FDP/D-dimer ratio in patients with DIC or PAVTE and patients without thrombosis. FDP, fibrinogen and fibrin degradation products; the D-dimer used a D-dimer C (LPIA-Genesis). ***; $p<0.001$, *, $p<0.050$

thrombosis tended to be lower for D-dimer kit with a low FDP/D-dimer ratio than for that with a high FDP/D-dimer ratio, suggesting that using a D-dimer kit with a low FDP/D-dimer ratio may result in an overdiagnosis of thrombosis.

When using a D-dimer C with a high FDP/D-dimer ratio, the FDP/D-dimer ratio proved useful for diagnosing DIC or PAVTE. Therefore, if we measure both FDPs and D-dimer levels, a D-dimer kit with a high FDP/D-dimer ratio might be useful. If possible, both the FDP and D-dimer levels should be measured to ensure the accurate diagnosis of thrombosis and evaluation of fibrinolysis. The D-dimer kit with a high FDP/D-dimer ratio has a high slop ($\geq$1.5) of the correlation line with FDP. As many FDP and D-dimer kits exist, a standardized FDP/D-dimer ratio will be difficult to establish. Furthermore, the usefulness of FDP/D-dimer ratio has not been determined. A large-scale investigation of FDP/D-dimer ratio is thus required. The cut off value of the FDP/D-dimer ratio may be recommended as $\geq$1.5 of LPIA-ACE D-Dimer II which is one of the most common for a D-dimer kit.

In conclusion, the plasma levels of D-dimer and the FDP/D-dimer ratio determined using three D-dimer kits varied among underlying diseases, and the utility of a D-dimer kit with a high FDP/D-dimer ratio was suggested.

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Declaration of Conflicting Interests

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ORCID iD

Hideo Wada https://orcid.org/0000-0001-9021-8633

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