Clinical and Applied Thrombosis/Hemostasis
Volume 26: 1-6

DOI: 10.1177/1076029620973084
journals.sagepub.com/home/cat

Elevated D-Dimer Levels Predict a Poor Outcome in Critically Ill Patients

Yuhuko Ichkawa, Ms[1], Hideo Wada, MD, PhD[1,2], Minoru Ezaki, Mr[1], Motoko Tanaka[1], Shinya Hiromori[1], Katsuya Shiraki, MD, PhD[1,2], Isao Moritani, MD, PhD[3], Akitaka Yamamoto, MD, PhD[4], Haruhiko Tashiro, MD, PhD[4], Hideto Shimpo, MD, PhD[5], and Motomu Shimaoka[6]

Abstract

D-dimer is a biomarker of thrombosis and recently been considered to predict a poor outcome in patients with infectious diseases. Plasma D-dimer levels were measured in critically ill patients to examine their relationship with the poor outcome. The plasma D-dimer levels were markedly higher in the patients with various underlying disease especially venous thromboembolism in comparison to those without severe underlying diseases. The plasma D-dimer levels in non-survivors were significantly higher than those in survivors. In a receiver operating characteristic analysis, the area under the curve was high for the disseminated intravascular coagulation (DIC) score, the D-dimer value, and the prothrombin time-international normalize ratio (PT-INR). Adequate cut-off values for predicting the outcome were 3 as follows: DIC score, 3 points; D-dimer, 4.2 mg/L; and PT-INR, 1.08. D-dimer, which is a biomarker for thrombosis, is increased in various underlying diseases and predicts a poor outcome.

Keywords

D-dimer, critically ill patients, poor outcome, thrombosis

Introduction

Fibrin-related markers (FRMs) such as fibrinogen and fibrin degradation products (FDPs), D-dimer and soluble fibrin (SF) are considered useful for diagnosing thrombotic diseases such as venous thromboembolism (VTE)[1,2] and disseminated intravascular coagulation (DIC).[3,4] Although elevated FRM levels can be used to predict the incidence of DVT after THA or TKA without anticoagulants,[5] their utility in predicting postoperative VTE is lost after the administration of fondaparinux or edoxaban.[6-8] FRM levels can also be used to diagnose VTE; however, adequate cut-off values for predicting thrombosis have not been established. A D-dimer assay is used as an initial screening test in the emergency department to exclude PE in Europe and North America.[9] The purpose of this test, which has a high negative predictive value (NPV), is to provide a fast and cost-effective way to triage patients with suspected PE for imaging tests.[9,10] It was recently reported that mild D-dimer elevation suggested an increased risk of subclinical and postoperative VTE.[6] In addition, elevated D-dimer levels have been reported to suggest massive bleeding in patients undergoing major operations.[8]

Several studies[11-13] on coronavirus disease 2019 (COVID-19) reported that D-dimer elevation might be associated with a high risk of a poor prognosis. As D-dimer elevation has attracted attention as a prognostic biomarker for COVID-19 pneumonia[13,14] and due to its association with thrombosis,[15] it has also been considered as a high-risk factor in critically ill

[1] Department of Central Laboratory, Mie Prefectural General Medical Center, Yokkaichi, Japan
[2] Associated Department with Mie Graduate School of Medicine, Tsu, Japan
[3] Department of General Medicine, Mie Prefectural General Medical Center, Yokkaichi, Japan
[4] Department of Emergency and Critical Care Center, Mie Prefectural General Medical Center, Yokkaichi, Japan
[5] Mie Prefectural General Medical Center, Yokkaichi, Japan
[6] Department of Molecular Pathobiology and Cell Adhesion Biology, 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

Table 1. Subjects.

	Age	Sex (F: M)	D-dimer (mg/L)	APTT (seconds)	PT-INR	PLT ($\times 10^9$/L)	CRP	WBC ($\times 10^6$/L)	Death
IFN	78.0 (63.0-83.0)	45:45	3.6*** (1.4-8.9)	32.0* (28.5-36.0)	1.09*** (1.03-1.19)	21.1 (15.6-28.9)	9.7*** (3.3-17.0)	10500*** (7600-14700)	10 (11.1%)
CT	73.0 (64.0-84.0)	17:32	1.2** (0.5-2.1)	29.0 (27.0-33.0)	0.97 (0.92-1.01)	20.7 (17.8-36.0)	0.18 (0.06-0.56)	8000 (6225-9375)	3 (6%)
HF	80 (75.5-90.0)	11:21	3.6*** (1.3-8.0)	31.0 (28.3-34.8)	1.09*** (0.99-1.07)	18.3 (15.0-29.4)	0.54*** (0.19-2.49)	7400 (5050-33325)	2 (6%)
DD	68.5 (54.0-83.0)	8:18	1.6*** (0.5-3.6)	28.0* (25.0-30.0)	0.98 (0.93-1.60)	24.3 (19.6-27.9)	0.29* (0.10-0.98)	10100** (6700-12700)	1 (4%)
HD	70.0 (51.0-83.0)	13:13	1.0* (0.5-2.4)	30.5 (27.0-34.0)	1.02* (0.94-1.07)	13.7*** (5.5-19.1)	0.17 (0.02-2.86)	5000** (3800-7900)	0 (0%)
HS	72.0 (42.0-88.0)	12:10	1.10* (0.5-2.7)	29.0 (27.0-31.3)	0.97 (0.94-1.29)	24.2 (20.6-28.1)	0.33 (0.05-1.13)	7650 (6100-10200)	1 (5%)
Trauma	69.0 (44.3-81.5)	11:10	8.3*** (3.6-41.8)	28.0 (26.0-34.3)	0.96 (0.92-1.07)	24.0 (16.1-32.0)	0.44** (0.15-1.22)	10100* (6900-11525)	2 (10%)
AA	74.0 (54.5-78.8)	9:10	5.3*** (2.9-14.4)	29.5 (26.9-40.0)	1.06*** (1.00-1.30)	19.2 (17.1-23.1)	0.29** (0.14-2.02)	8100 (5200-9475)	1 (5%)
SC	71.0 (51.8-78.0)	10:7	4.3*** (2.7-34.8)	31.0 (27.3-37.8)	1.09** (0.95-1.38)	20.9 (13.5-28.5)	2.56*** (0.30-7.68)	9100* (8350-11250)	5 (29%)
IB	73.0 (51.8-82.5)	6:11	1.6*** (0.6-3.8)	27.0 (25.0-33.5)	0.99 (0.94-1.04)	22.9 (19.9-28.5)	0.18 (0.08-0.74)	9100 (5800-16650)	5 (29%)
AMI	76.0 (67.0-90.0)	7:8	1.1* (0.5-2.7)	32.0 (29.0-38.0)	1.03 (0.94-1.18)	19.1 (14.0-24.9)	0.65* (0.08-1.51)	8300 (5625-9875)	1 (7%)
CPA	83.0 (74.5-87.8)	4:11	36.8*** (11.0-74.7)	58.0*** (42.8-81.8)	1.49*** (1.24-1.65)	9.6*** (6.7-15.0)	0.59** (0.30-3.3)	10200* (7000-14875)	14 (93%)
VTE	62.0 (56.3-70.3)	4:7	11.1*** (0.9-15.8)	34.0* (31.3-37.0)	1.05** (0.98-1.12)	23.2 (19.2-26.4)	0.90* (0.07-6.01))	6400 (6200-7925)	0 (0%)
Others	66.0 (38.3-81.0)	34:41	1.6*** (0.6-3.7)	28.5 (27.0-31.0)	0.97 (0.94-1.04)	22.4 (18.5-29.2)	0.29* (0.07-1.13)	8300 (5475-10750)	3 (4%)
NSUD	61.0 (47.5-74.0)	20:17	0.5 (0.5-1.1)	29.0 (28.0-32.0)	0.96 (0.94-1.00)	25.8 (20.3-29.0)	0.09 (0.04-0.32)	7000 (6000-9225)	0 (0%)

NSUD, no severe underlying disease; INF, infection; CT, cerebral thrombosis; HF, heart failure; DD, digestive disease; HD, hematological disease; HS; heat stroke; AA, aortic aneurysm; SC, solid cancer; IB, intracranial bleeding; CPA, cardiopulmonary arrest.
***, $p < 0.001$ in comparison with NSUD; **, $p < 0.01$ in comparison with NSUD; *, $p < 0.05$ in comparison with NSUD.

patients. Critically ill disease includes infectious disease, trauma, heart failure, thrombotic disease such as cerebral thrombosis, acute myocardial infarction (AMI), venous thromboembolism (VTE), intracranial bleeding, and other conditions. The behavior of D-dimer levels in the above diseases is interesting and predictive of the outcome.

In this study, plasma D-dimer levels were examined in critically ill patients with various diseases and the relationship between D-dimer levels and the outcomes of 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; no severe underlying disease (NSUD), n = 37; infectious disease, n = 90; cerebral thrombosis, n = 49; heart failure, n = 33; digestive disease, n = 26; hematological disease, n = 26; heat stroke, n = 22; trauma, n = 21; aortic aneurysm, n 19; solid cancer, n = 17; intracranial bleeding, n = 17; AMI, n = 15; cardiopulmonary arrest (CPA), n = 15; VTE, n = 11; other diseases, n = 75 (Table 1). Cerebral thrombosis, AMI and VTE were considered thrombotic diseases.

The plasma D-dimer, fibrinogen and c-reactive protein (CRP) levels, activated partial thromboplastin time (APTT), prothrombin time (PT)-international normalized ratio (INR), white blood cell (WBC) count, hemoglobin (Hb) and platelet count were measured in 470 critically ill patients, when they were admitted to the intensive-care unit or when outpatients first arrived at our hospital. The D-dimer and fibrinogen levels and APTT and PT-INR were measured using an automatic coagulation analyzer (CS-5100, Sysmex, Kobe, Japan) using LIASAUTO D-dimer Neo, Thrombocheck Fib (L) and Thrombocheck APTT-SLA T (Sysmex), and Thromborel S (Siemens Healthcare Diagnostics Products GmbH, Malvern, USA).

The normal median (25th-75th percentile) value and negative predictive values for DVT of D-dimer were 0.30 μg/ml (0.10-0.50 μg/ml) and 1.2 μg/ml, respectively.[16]

The WBC count, Hb level and platelet count were measured by a full automatic blood cell analyzer XN-3000 (Sysmex) and CRP was measured using a Hitachi Labospect 006 (Hitachi, Tokyo, Japan) using a CRP-Latex X2-Seiken (DenkaSeiken Co, Niigata, Japan). The DIC score was determined using the

scoring system established by the Japanese Ministry of Health, Labor and Welfare (JMHLW).[3]

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. P values of <0.05 were considered to indicate a statistically significance. All of the statistical analyses were performed using the Stat-Flex software program (version 6; Artec Co Ltd, Osaka, Japan). The cut-off values were examined by a receiver operating characteristic (ROC) analysis.

Results

The plasma D-dimer levels in patients with the following conditions were significantly higher than those in patients with NSUD: infectious disease ($p < 0.001$), thrombotic disease ($p < 0.001$), heart failure ($p < 0.001$), digestive disease ($p < 0.001$), hematological disease ($p < 0.05$), heat shock ($p < 0.05$), trauma ($p < 0.001$), aortic aneurysm ($p < 0.001$), solid cancer ($p < 0.001$), intracranial bleeding ($p < 0.001$), CPA ($p < 0.001$) and other diseases ($p < 0.001$) (Figure 1 and Table 1). Among patients with thrombotic disease, the plasma D-dimer levels in the patients with the following conditions were significantly higher than those in patients with NSUD: VTE ($p < 0.001$), cerebral thrombosis ($p < 0.01$) and AMI ($P < 0.05$) (Figure 2). The APTTs in patients with the following conditions were significantly longer in comparison to those with NSUD: CPA ($p < 0.001$), infectious disease ($p < 0.05$) and VTE ($p < 0.05$) (Table 1). The PT-INRs in patients with the following conditions were significantly higher in comparison to those with NSUD: infectious disease ($p < 0.001$), heart failure ($p < 0.001$), aortic aneurysm ($p < 0.001$), CPA ($p < 0.001$), VTE ($p < 0.001$), solid cancer ($p < 0.01$) and hematological disease ($p < 0.05$). The Platelet counts in patients with hematological disease ($p < 0.001$) and those with CPA ($p < 0.001$) were significantly lower in comparison to those with NSUD. The CRP levels in patients with the following conditions were significantly higher than those in patients with NSUD: infectious disease ($p < 0.001$), heart failure ($p < 0.001$), solid cancer ($p < 0.001$), trauma ($p < 0.01$), aortic aneurysm ($p < 0.01$), CPA ($p < 0.01$), digestive disease ($p < 0.05$), AMI ($p < 0.05$), VTE ($p < 0.05$) and others ($p < 0.05$). The WBC counts in patients with the following conditions were significantly higher than those in patients with NSUD: infectious disease ($p < 0.001$), digestive disease ($p < 0.01$), trauma ($p < 0.05$), solid cancer ($p < 0.05$) and CPA ($p < 0.05$). In contrast WBC counts in the patients with hematological disease and significantly lower in comparison to those with NSUD ($p < 0.01$).

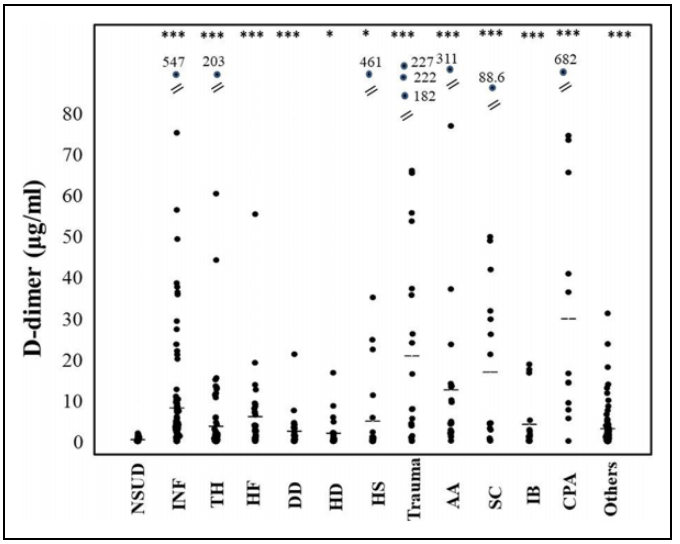

Figure 1. Plasma D-dimer levels in various underlying diseases. NSUD, no severe underlying disease; INF, infection; TH, thrombotic disease; HF, heart failure; DD, digestive disease; HD, hematological disease; Hs, heat stroke; AA, aortic aneurysm; SC, solid cancer; IB, Intracranial bleeding; CPA, cardiopulmonary arrest. *** $p < 0.001$ in comparison to NSUD; * $p < 0.05$ in comparison to NSUD.

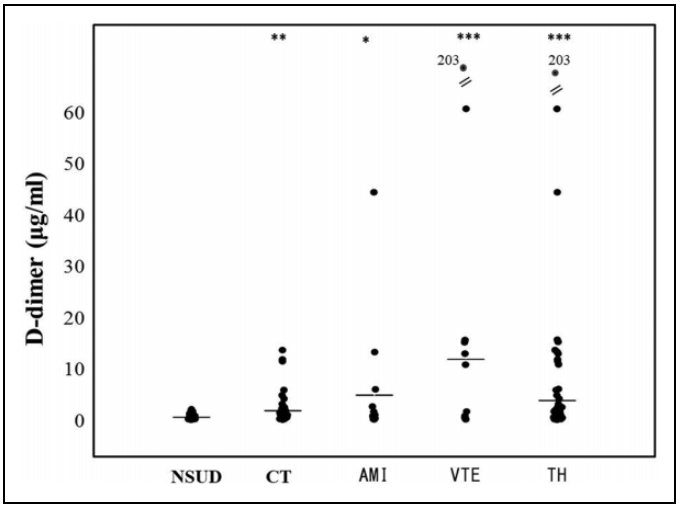

Figure 2. Plasma D-dimer levels in various underlying diseases. NSUD, no severe underlying disease; CT, cerebral thrombosis; AMI, acute myocardial infarction; VTE, venous thromboembolism; TH, thrombotic disease. ***, $p < 0.001$ in comparison to NSUD; **, $p < 0.01$ in comparison to NSUD; *, $p < 0.05$ in comparison to NSUD.

Age ($p < 0.001$), PT-INR ($p < 0.001$), WBC ($p < 0.01$), and the DIC score were significantly higher in non-survivors than survivors. In non-survivors, the APTT ($p < 0.001$) was significantly longer, the D-dimer ($p < 0.001$) and CRP ($p < 0.01$) levels were significantly higher, and the Hb levels ($p < 0.01$) and platelet counts ($p < 0.001$) were significantly lower in comparison to survivors (Table 2).

In a ROC analysis of non-survivors versus survivors, the highest area under the curve (AUC) value was 0.903 in DIC

Table 2. Hemostatic Markers in Survivors and Non-Survivors.

	Survivors	Non-survivors	
Age (years)	71.0 (51.0-83.0)	79.0 (73.0-84.3)	P < 0.001
Sex	193: 228	17: 32	
APTT (sec)	30.0 (27.0-34.0)	36.0 (29.0-54.5)	P < 0.001
PT-INR	1.00 (0.95-1.09)	1.19 (1.07-1.61)	P < 0.001
Fibrinogen (g/L)	3 (2.48-3.73)	2.83 (1.85-3.57)	Not significant
D-dimer (mg/L)	1.6 (0.6-4.7)	17.0 (4.20-39.6)	P < 0.001
CRP	0.44 (0.09-3.54)	1.62 (0.29-8.86)	P < 0.01
White blood cell count ($\times 10^8$/L)	83 (60-112)	97 (69-148)	P < 0.05
Hemoglobin (g/L)	125 (111-143)	111 (968-136)	P < 0.01
Platelet count ($\times$ 10^9/L)	218 (171-283)	178 (99-230)	P < 0.001
DIC score	1.0 (0.0-2.0)	5.0 (2.0-7.0)	P < 0.001

Table 3. The Receiver Operating Characteristics Analysis of Several Markers for Predicting a Poor Outcomes in Critically ill Patients.

	Cutoff value	AUC	Sensitivity	Odds ratio
Age	77.0 years	0.661	0.630	2.926
APTT	31.2 seconds	0.685	0.646	3.238
PT-INR	1.08	0.749	0.721	6.651
Fibrinogen	2.77g/L	0.587	0.556	1.549
D-dimer	4.2 mg/L	0.803	0.729	7.369
CRP	0.909	0.623	0.604	2.342
White blood cell count	90 $\times$ 10^8/L	0.606	0.583	2.162
Hemoglobin	121	0.625	0.608	2.431
Platelet count	201 $\times$ 10^9/L	0.671	0.590	2.082
DIC score	3 points	0.903	0.800	13.45

The cut-off points was set as the points at which the sensitivity and specificity curves crossed according to a receiver operating characteristics analysis. APTT, activated partial thromboplastin time; PT, prothrombin time; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; AUC, area under the curve.

score, 0.803 in D-dimer and 0.749 in PT-INR. The sensitivity and odds ratio were also high for the JMHLW DIC score, D-dimer, and PT-INR (Table 3). The sensitivity and odds ratio were low for the platelet count and fibrinogen levels. The following cut-off value were considered adequate: JMHLW DIC score, 3 points; and D-dimer, 4.2 mg/L according to the ROC analysis (Figure 3). The distribution of plasma D-dimer levels between survivors and non-survivors is shown in Figure 4. These data showed little overlap with D-dimer $\geq$ 4.2μg/ml between survivors and non-survivors.

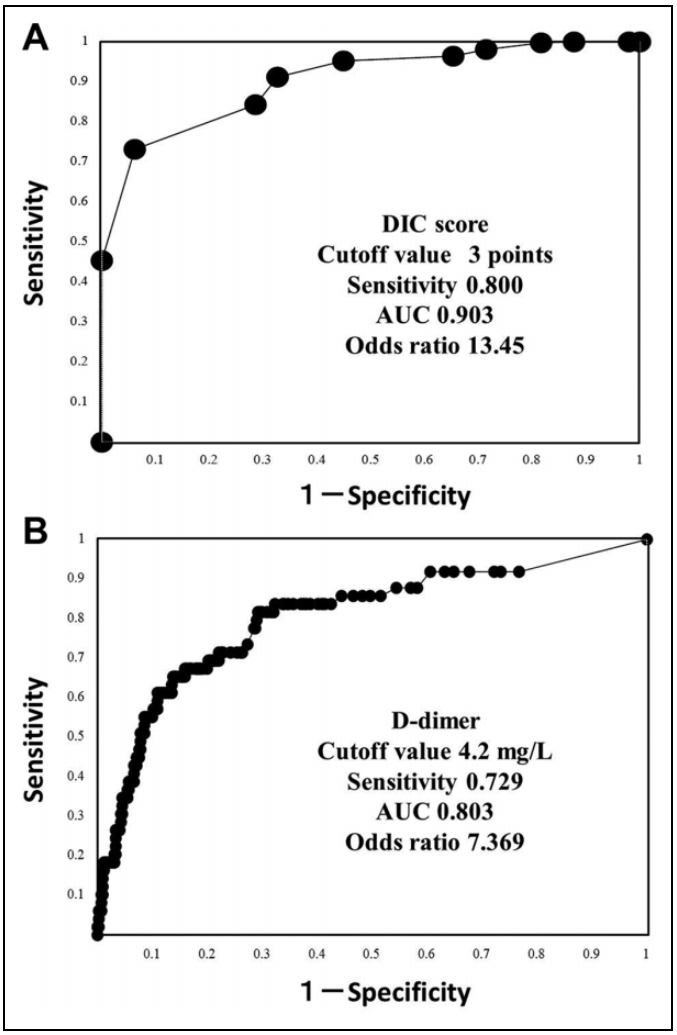

Figure 3. The receiver operating characteristics analysis of the DIC score (A) and D-dimer levels (B) for predicting the outcomes in critically ill patients. DIC, disseminated intravascular coagulation; AUC, area under the curve. The cut-off point was set as the point at which the sensitivity and specificity curves crossed according to a receiver operating characteristics analysis. The DIC score was determined using the scoring system established by the Japanese Ministry Health Labor and Welfare.

Discussion

The plasma D-dimer levels in patients with NSUD were 0.5 (0.5-1.1) (mg/L) and not markedly increased; thus, these values could be used as a control for the comparison of patients with various underlying diseases or conditions. The plasma D-dimer levels were significantly high in patients with the following conditions: infection and thrombotic disease, trauma, aortic aneurysm, heart failure and CPA. Infection, trauma, aortic

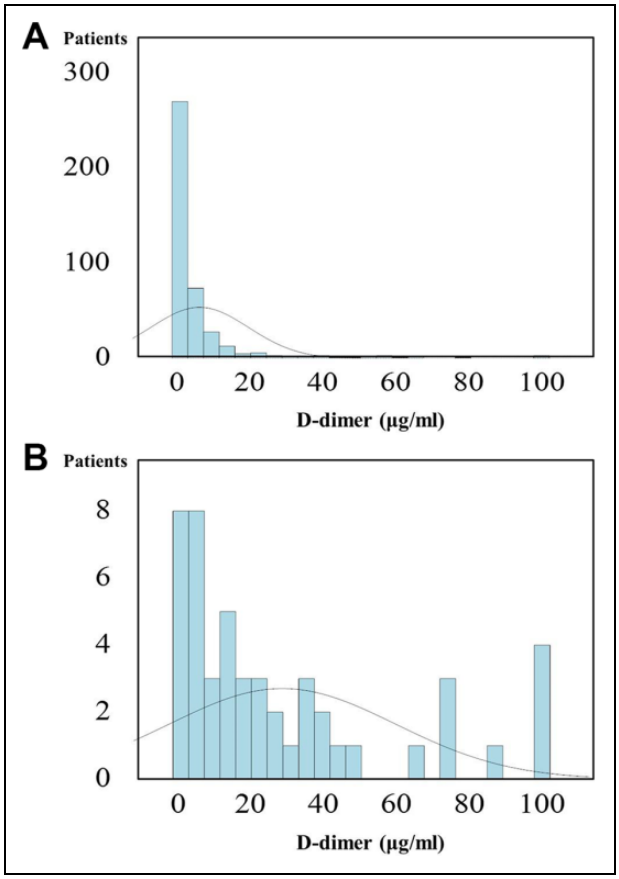

Figure 4. Distribution of plasma D-dimer levels between survivors (A) and non-survivors (B).

aneurysm and CPA were frequently associated with DIC[17,18]; elevated D-dimer levels were previously reported to be associated with these diseases.[19,20] Heart failure is not usually associated with DIC; however, elevated D-dimer levels were observed in patients with heart failure in the present study and in previous studies.[21] The mechanism of D-dimer elevation in patients with heart failure was reported to involve hemostatic abnormality and to predict a poor outcome. In this study, there were many trauma patients without organ failure who only had simple bone fracture. These findings suggest that D-dimer elevation might be caused by bone fracture. Although D-dimer elevation has been reported in patients who received major orthopedic surgery,[6,8] elevated D-dimer levels may not only be caused by hemostasis and thrombosis due to surgery, but D-dimer may also be released from operated bone. Thus, the evaluation of D-dimer elevation for the diagnosis of DIC or venous thrombosis may be difficult for patients with heart failure or bone fracture.

Although the D-dimer levels were high in patients with thrombotic diseases, these levels were not high in patients with AMI and varied in the patients with cerebral infarction. As most AMI[22] caused by the rupture of atheromatous plaques due to activation of platelets or spasm, plasma D-dimer levels were not markedly increased in the patients with AMI. As cerebral thrombosis is caused by several mechanisms, including the rupture of atheromatous plaques, thrombophilia or embolism from the heart, the D-dimer levels varied among patients with cerebral thrombosis, suggesting that the detection of elevated D-dimer levels may be useful for the adaptation of anticoagulant therapy in some patients with cerebral thrombosis.

D-dimer elevation was not included in the scoring system to diagnose sepsis-induced coagulopathy.[23,24] However, in this study, the D-dimer levels were significantly higher in patients with infectious diseases. The DIC score showed the strongest relationship with the outcome, followed by the D-dimer level. As FRMs including the D-dimer level, are the most important markers in the scoring of DIC, critically ill patients who demonstrated elevated D-dimer levels may therefore have a poor outcome due to the association of DIC.

In conclusion, D-dimer is increased in various underlying diseases, and elevated D-dimer levels predicts a poor outcome in critically ill patients.

Acknowledgments

We thank the many technicians at Central Laboratory for measuring the laboratory data and the many physicians who took care of the critically ill patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported in part by a Grant-in-Aid from the Ministry of Health, Labour.

ORCID iD

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

References

1. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *JAMA*. 2014;311(11):1117-1124.
2. Wada H, Kobayashi T, Abe Y, et al. Elevated levels of soluble fibrin or D-dimer indicate high risk of thrombosis. *J Thromb Haemost*. 2006;4(6):1253-1258.
3. Wada H, Matsumoto T, Yamashita Y, Hatada T. Disseminated intravascular coagulation: testing and diagnosis. *Clin Chim Acta*. 2014;436C:130-134.
4. Wada H, Thachil J, Di Nisio M, et al. The scientific standardization committee on DIC of the International Society on Thrombosis Haemostasis: guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. *J Thromb Haemost*. 2013;11:761-767.
5. Sudo A, Wada H, Nobori T, et al. Cut-off values of D-dimer and soluble fibrin for prediction of deep vein thrombosis after orthopaedic surgery. *Int J Hematol*. 2009;89(5):572-576.

6. Yamaguchi T, Wada H, Miyazaki S, et al. Fibrin related markers for diagnosing acute or chronic venous thromboembolism in patients with major orthopedic surgery. *Int J Hematol*. 2016; 103(5):560-566.
7. Yoshida K, Wada H, Hasegawa M, et al. Monitoring for anti-Xa activity for prophylactic administration of fondaparinux in patients with artificial joint replacement. *Int J Hematol*. 2011; 94(4):355-360.
8. Hasegawa M, Wada H, Wakabayashi H, et al. The relationships among hemostatic markers, the withdrawal of fondaparinux due to a reduction in hemoglobin and deep vein thrombosis in Japanese patients undergoing major orthopedic surgery. *Clin Chim Acta*. 2013;425:109-113.
9. Geersing GJ, Zuithoff NP, Kearon C, et al. Exclusion of deep vein thrombosis using the Wells rule in clinically important subgroups: individual patient data meta-analysis. *BMJ*. 2014;348:g1340.
10. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med*. 2003;349(13):1227-1235.
11. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054-1062.
12. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099.
13. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069.
14. Phelan AL, Katz R, Gostin LO. The novel coronavirus originating in Wuhan, China: challenges for global health governance. *JAMA*. 2020;323(8):709-710.
15. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145-147.
16. Hasegawa M, Wada H, Miyazaki S, et al. The evaluation of fibrin-related markers for diagnosing or predicting acute or subclinical venous thromboembolism in patients undergoing major orthopedic surgery. *Clin Appl Thromb Hemost*. 2018;24(1):107-114.
17. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. *J Intensive Care*. 2014;2(1):15.
18. Wada H, Matsumoto T, Hatada T. Diagnostic criteria and laboratory tests for disseminated intravascular coagulation. *Expert Rev Hematol*. 2012;5(6):643-652.
19. Okamoto K, Wada H, Hatada T, et al. Japanese Society of Thrombosis Hemostasis/DIC subcommittee: frequency and hemostatic abnormalities in pre-DIC patients. *Thromb Res*. 2010;126(1):74-78.
20. Kawano N, Wada H, Uchiyama T, et al. Analysis of the association between resolution of disseminated intravascular coagulation (DIC) and treatment outcomes in post-marketing surveillance of thrombomodulin alpha for DIC with infectious disease and with hematological malignancy by organ failure. *Thromb J*. 2020;18(1):2.
21. Yan W, Liu J, Liu H, et al. Elevated D-dimer levels predict adverse outcomes in hospitalised elderly patients with chronic heart failure. *Intern Med J*. 2019;49(10):1299-1306.
22. Reihani H, Shamloo AS, Keshmiri A. Diagnostic value of D-Dimer in acute myocardial infarction among patients with suspected acute coronary syndrome. *Cardiol Res*. 2018;9(1):17-21.
23. Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M. Scientific and standardization Committee on DIC, and the Scientific and Standardization Committee on Perioperative and Critical Care of the International Society on Thrombosis and Haemostasis: diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. *J Thromb Haemost*. 2019;17(11):1989-1994.
24. Wada H, Shiraki K, Shimaoka M. The prothrombin time ratio is not a more effective marker for evaluating sepsis-induced coagulopathy than fibrin-related markers. *J Thromb Hemost*. 2020; 18(6):1506-1507.