D-dimer predicts poor hospitalisation outcomes in patients with antineutrophil cytoplasmic autoantibody-associated vasculitis

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ABSTRACT

Objective. *The in-hospital mortality rate among patients with antineutrophil cytoplasmic autoantibody-associated vasculitis (AAV) is high. Unfortunately, there is no reliable prognostic biomarker. This study aimed to investigate whether elevated D-dimer levels can predict hospitalisation outcomes among patients with AAV.*

Methods. *We performed a retrospective analysis at a tertiary medical centre in Seoul, South Korea, between 2005 and 2019. Patients with AAV requiring hospitalisation, whose D-dimer levels were available within one week of hospitalisation, were included; patients with known alternative reasons for elevated D-dimer were excluded. Death and intensive care unit requirements were defined as adverse outcomes.*

Results. *In total, 61 AAV patients with a total of 100 episodes of hospitalisation were included. Median D-dimer levels were significantly higher in patients with adverse outcomes than in those without adverse outcomes (1.84 vs. 0.42 mg/dL; p=0.006). Consistently, the incidence of the adverse outcomes was significantly higher in the high D-dimer group (≥0.699 mg/dL; n = 40) than in the low D-dimer group (<0.699 mg/dL; n = 60) (35% vs. 10%; p=0.002). Multivariate logistic regression analysis revealed that a high D-dimer level was a significant risk factor for adverse outcomes (hazard ratio, 4.852; 95% confidence interval, 1.320-17.833; p=0.017). Kaplan-Meier survival analysis revealed that the high D-dimer group was associated with more 30-day in-hospital adverse outcomes than the low D-dimer group (p=0.008).*

Conclusion. *High D-dimer levels on admission are significantly associated with adverse outcomes among patients with AAV.*

Introduction

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is a group of systemic vasculitides, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). AAV can be fatal if not appropriately treated in the early stages (1, 2). Common causes of death are disease progression itself and secondary infections associated with the use of immunosuppressants (3). Scoring systems, including the Birmingham Vasculitis Activity Score (BVAS), Five-Factor Score (FFS), and Vasculitis Damage Index, are currently available to quantify the burden of AAV (4-6); however, their clinical application is limited in predicting the disease mortality and prognosis at the time of admission. Therefore, a reliable biomarker is urgently required to assess the prognosis of AAV upon hospitalisation.

D-dimer is a fibrin degradation product associated with endothelial activation (7). The D-dimer level is associated with several vascular diseases, including deep vein thrombosis, pulmonary embolism, pulmonary hypertension, and peripheral arterial disease (8-10). D-dimer levels on admission are also linked to the inflammatory burden in acute pancreatitis and community-acquired pneumonia (11, 12). Further evidence indicates that D-dimer potentially contributes to immune function in neutrophils, platelets, and neutrophil extracellular traps (NETs) (13, 14).

We hypothesised that D-dimer levels at the time of admission could predict poor hospitalisation outcomes, such as death or transfer to the intensive care unit (ICU), among patients with AAV. This study aimed to investigate the association between D-dimer levels and hospitalisation outcomes in patients with AAV.

Materials and methods

Study population

We retrospectively analysed the association between D-dimer and the poor hospitalisation outcomes among patients with AAV hospitalised at Severance Hospital, Yonsei University Health System, a tertiary medical centre in Seoul, Republic of Korea, between January 2005 and May 2019. We included 61 patients presenting 100 episodes of hospitalisation owing to vasculitis, whose D-dimer levels were available within the first week of their hospitalisation. All patients had a prior or new diagnosis of AAV at the time of their hospitalisation in accordance with the 2007 European Medicine Agency algorithms or the 2012 Chapel Hill Consensus Conference Nomenclature of Vasculitides (15, 16). Patients were excluded if they had conditions that have strong associations with an elevated D-dimer, such as thromboembolic disease, chronic liver disease, heart failure, infection, or malignancy on admission. Patients with suspected thrombosis in the CT scans or suspected thrombosis symptoms were excluded from this study. There were no incidental events of thrombosis during hospitalisation. None of the patients included in this study received anticoagulation treatment. This study was approved by the Institutional Review Board of Severance Hospital (IRB protocol number 4-2016-0967). The need for informed consent was waived by the Institutional Review Board due to the study's retrospective nature.

Table I. Baseline characteristics of patients with AAV with and without in-hospital adverse outcomes.

Variable§	All episodes (n=100)	Without adverse outcomes (n=80)	With adverse outcomes (n=20)	*p*-value
Age	64.0 (46.0–72.0)	63.0 (43.0–70.0)	69.0 (54.0–75.0)	0.035
Male sex, n (%)	43 (43.0)	33 (41.3)	10 (50.0)	0.480
Diagnosis GPA	28	19	9	0.153
MPA	55	46	9	
EGPA	17	15	2	
Disease duration (months)	2.0 (0.0-40.8)	1.5 (0.0-30.8)	7.0 (0.0-78.5)	0.088
Hospital stay (days)	12.0 (4.0–23.0)	10.0 (3.0–18.0)	25.0 (10.0–82.0)	<0.001
Underlying comorbidities				
Diabetes mellitus (%)	21 (21.0)	17 (21.3)	4 (20.0)	0.902
Hypertension (%)	53 (53.0)	44 (55.0)	9 (45.0)	0.423
CKD (stage 3-5) (%)	25 (25.0)	21 (26.3)	4 (20.0)	0.564
Dyslipidaemia (%)	16 (16.0)	13 (16.3)	3 (15.0)	0.892
Disease activity index				
FFS	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (2.0–3.0)	0.044
BVAS	12.0 (10.0–16.0)	12.0 (10.0–15.0)	16.0 (9.0–18.0)	0.088
Severe flare-up by BVAS (%)	52 (52.0)	39 (48.8)	13 (65.0)	0.193
Laboratory findings				
Urine protein creatinine ratio	1.1 (0.5-2.6)	1.0 (0.4-2.5)	1.8 (0.6-7.9)	0.220
INR	0.98 (0.90–1.12)	0.98 (0.90–1.11)	1.00 (0.94–1.21)	0.177
Fibrinogen (mg/dL)	410 (335–534)	421 (336–495)	399 (271–669)	0.873
D-dimer (mg/dL)	0.56 (0.25–1.31)	0.42 (0.21–0.95)	1.84 (0.69–2.43)	< 0.001
Positive MPO-ANCA or P-ANCA, n (%)	74 (74.0)	61 (76.3)	13 (65.0)	0.305
Positive PR3-ANCA or C-ANCA, n (%)	19 (19.0)	13 (16.3)	6 (30.0)	0.161
BUN (mg/dL)	24.1 (15.1–42.3)	23.6 (15.1–42.3)	29.4 (15.2–43.4)	0.526
Creatinine (mg/dL)	1.1 (0.8–2.8)	1.1 (0.8–3.1)	1.4 (0.8–2.5)	0.849
WBC (/μL)	8,850 (6,120–12,795)	8,970 (6,070–12,005)	8,640 (7,270–13,720)	0.816
Haemoglobin (g/dL)	11.1 (9.2–12.0)	11.0 (9.3–12.0)	11.3 (9.0–12.1)	0.826
Platelet (10^3/μL)	237 (173–315)	248 (281–321)	200 (129–254)	0.044
ESR (mm/h)	58 (28–85)	58 (28–83)	60 (33–88)	0.744
CRP (mg/L)	29.2 (2.9–89.4)	21.0 (2.6–72.2)	99.2 (26.4–131.8)	0.001

Values are expressed as medians (interquartile ranges, IQR) or numbers (percentages).
AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; CKD: chronic kidney disease; BVAS: Birmingham Vasculitis Activity Score; FFS: Five-Factor Score; MPO myeloperoxidase; P: perinuclear; PR-3: proteinase 3; C: cytoplasmic; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Baseline demographic characteristics, clinical manifestations, and organ involvement

We obtained the baseline demographics and laboratory data, including complete blood count, biochemical tests, proteinuria, haematuria, creatinine clearance, prothrombin time/international normalised ratio, fibrin degradation products, and fibrinogen. We reviewed the clinical findings of the patients, *i.e.* constitutional symptoms of the BVAS assessment items, including arthralgia/arthritis, skin rash, fever, and organ involvement. Severe flares (*i.e.* the occurrence of any new/worse major item) and limited flares (*i.e.* the occurrence of any new/worse minor item) on the BVAS were evaluated (4). Organ involvement was evaluated based on the revised FFS (5).

Evaluation of poor hospitalisation outcomes

We evaluated hospitalisation outcomes using the hospital's electronic medical records. We recorded occurrences of in-hospital adverse outcomes, which are death and ICU admission following hospitalisation. In-hospital death was determined as any cause of death. The cause of death was also evaluated.

Quantification of D-dimer and ANCA levels

When AAV patients were hospitalised with systemic inflammatory manifestations, D-dimer levels were assessed by the caring physicians for the screening of various conditions that cause endothelial dysfunction and vasculopathy, such as thrombosis, infections, and vasculitis. D-dimer levels were quantified using HemosIL D-dimer HS for ACL TOP (Bedford, MA, USA), a latex-enhanced turbidimetric immunoassay, in accordance with the manufacturer's instructions. Perinuclear (P)-ANCA, cytoplasmic (C)-ANCA, myeloperoxidase (MPO)-ANCA, and proteinase 3 (PR3)-ANCA levels were determined through standard indirect immunofluorescence and an enzyme-linked immunosorbent assay kit (Thermo Fisher Scientific,

Freiburg, Germany) in accordance with the manufacturer's instructions.

Statistical analyses

Continuous variables are expressed as the median (quartile range) or percentage. A receiver operating characteristic (ROC) curve was used to identify a D-dimer cut-off that predicted the adverse outcome with the highest sensitivity and specificity. Based on this cut-off value, patients were then divided into two groups: high D-dimer and low D-dimer groups. The chi-square test, Fisher exact test, and Wilcoxon signed-rank test were performed to evaluate the differences between groups. Kaplan-Meier curves were created, and the log-rank test was performed to investigate the association between D-dimer levels and adverse outcomes. Censoring was carried out upon discharge. Cox proportional hazard regression analysis, including multiple factors associated with the in-hospital mortality rate, was performed to compute the hazard ratio (HR) among patients with AAV. All statistical analyses were performed using IBM SPSS Statistics 25.0 software (IBM SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Results

Clinical characteristics of patients with AAV

Among the 61 patients, there were 100 episodes of hospitalisation during the study period (Table I). The median time between hospitalisation and measurement of D-dimer was 0 (0.0-1.0) days. The baseline characteristics of patients with and without adverse outcomes are described in Table I. Among the 100 hospitalisation episodes, 20 episodes were related to adverse outcomes. There was no difference in the incidence of adverse outcomes among the three subtypes of AAV (GPA 32.1%, MPA 16.4%, and EGPA 11.8%). Disease duration was longer in patients with adverse outcomes but not statistically significant (7.0 *vs*. 1.5 months, p=0.088), and hospital stay was longer in patients with adverse outcomes than in those without adverse outcomes (25.0 *vs*. 10.0 days, p<0.001).

Table II. Clinical features of patients with AAV and organ involvement.

Organ involvement	All episodes (n=100)	Without adverse outcomes (n=80)	With adverse outcomes (n=20)	p-value
Individual organ involvement at the time of diagnosis (n, (%))				
Constitutional symptoms	39 (39.0)	31 (38.8)	8 (40.0)	0.918
Skin	10 (10.0)	6 (7.5)	4 (20.0)	0.096
Eyes	1 (1.0)	1 (1.3)	0 (0)	0.615
Ear, nose, throat	8 (8.0)	7 (8.8)	1 (5.0)	0.580
Lung	59 (59.0)	43 (53.8)	16 (80.0)	0.033
Cardiovascular	3 (3.0)	2 (2.5)	1 (5.0)	0.558
Gastrointestinal	10 (10.0)	7 (8.8)	3 (15.0)	0.405
Renal	76 (76.0)	59 (73.8)	17 (85.0)	0.292
Nervous system	27 (27.0)	22 (27.5)	5 (25.0)	0.822
Individual organ involvement that led to hospitalisation (n, (%))				
Constitutional symptoms	48 (48.0)	37 (46.3)	11 (55.0)	0.484
Skin	8 (8.0)	4 (5.0)	4 (20.0)	0.027
Eyes	1 (1.0)	1 (1.3)	0 (0)	0.615
Ear, nose, throat	7 (7.0)	7 (8.8)	0 (0.0)	0.170
Lung	53 (53.0)	38 (47.5)	15 (70.0)	0.028
Cardiovascular	2 (2.0)	1 (1.3)	1 (5.0)	0.284
Gastrointestinal	8 (8.0)	6 (7.5)	2 (10.0)	0.712
Renal	40 (40.0)	31 (77.5)	9 (45.0)	0.610
Nervous system	17 (17.0)	15 (18.8)	2 (10.0)	0.351
Multiple organ involvement based on revised FFS (n, (%))				
0	3 (3.0)	2 (2.5)	1 (5.0)	0.121
1	31 (31.0)	28 (35.0)	3 (15.0)	
2	39 (39.0)	32 (40.0)	7 (35.0)	
3	21 (21.0)	15 (18.8)	6 (30.0)	
4	5 (5.0)	2 (2.5)	3 (15.0)	
5	1 (1.0)	1 (1.3)	0 (0)	
FFS ≥3	27 (27.0)	18 (22.5)	9 (45.0)	0.043

AAV: ANCA-associated vasculitis; FFS: Five-Factor Score.

Table III. Pearson correlation analysis between D-dimer levels and disease activity markers of AAV.

	D-dimer	Albumin	WBC	Haemoglobin	ESR	CRP	BVAS	FFS
D-dimer	1							
Albumin	-0.456**	1						
WBC	0.141	-0.163	1					
Haemoglobin	-0.219*	0.515**	0.158	1				
ESR	0.108	-0.479**	0.111	-0.183	1			
CRP	0.298**	-0.526**	0.065	-0.141	0.573**	1		
BVAS	0.325**	-0.302**	0.099	-0.281**	0.214*	0.194	1	
FFS	0.337**	-0.372**	-0.124	-0.337**	0.063	0.070	0.282**	1

*p<0.05, **p<0.01.
WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BVAS: Birmingham Vasculitis Activity Score; FFS: Five-Factor Score.

Evaluation of disease activity indices demonstrated that patients with adverse outcomes had significantly higher FFS (p=0.044) than those without adverse outcomes. BVAS was also higher in the adverse outcome group than in the no-adverse outcome group, but this was not statistically significant (p=0.088). There was no statistical difference in the incidence of severe flare-up measured using BVAS between patients with and without adverse events.

Evaluation of laboratory findings demonstrated that D-dimer values were significantly higher in patients with adverse outcomes than in those without (1.84 *vs*. 0.42 mg/dL, p<0.001). The platelet count was significantly lower

in patients with adverse outcomes than in those without (200,000 *vs*. 248,000 counts/μL, *p*=0.044). C-reactive protein (CRP) levels were significantly higher in patients with adverse outcomes than those without (99.2 *vs*. 21.0 mg/L, *p*=0.001).

Evaluation of clinical features at the time of diagnosis demonstrated that lung involvement was significantly higher in patients with adverse outcomes than those without (80.0% *vs*. 53.8%, *p*=0.033) (Table II). Using the FFS to evaluate multiple organ involvement, FFS ≥3 was found to be significantly higher in patients with adverse outcomes than in those without (45.0% *vs*. 22.5%, *p*=0.043).

We also evaluated the clinical phenotypes that led to hospitalisation, which showed that skin and lung involvement were significantly higher in patients with adverse outcomes than in those without (20.0% *vs*. 5.0%, *p*=0.027; 70.0% *vs*. 47.5%, *p*=0.028, respectively) (Table II).

Incidence of adverse outcomes in high vs. low D-dimer groups

Analysis of ROC curves revealed that D-dimer levels of 0.699 mg/dL could predict adverse outcomes with the highest sensitivity (0.700) and specificity (0.675) (Supplementary Fig. S1). The area under the curve associated with adverse outcomes was 0.789 (95% confidence interval [CI] 0.689–0.890; *p*<0.001). Patients were divided into high D-dimer and low D-dimer groups using the threshold D-dimer level of 0.699 mg/dL. The incidence of adverse outcomes was significantly higher in the high D-dimer group than in the low D-dimer group (35.0% *vs*. 10.0%, *p*=0.002) (Fig. 1).

Association between D-dimer levels and disease activity markers of AAV

D-dimer levels were positively correlated with the CRP level (r=0.298), BVAS (r=0.325), and FFS (r=0.337) and negatively correlated with albumin (r=-0.456) and haemoglobin (r=-0.219) levels. However, D-dimer levels were not associated with the white blood cell count or erythrocyte sedimentation rate (Table III).

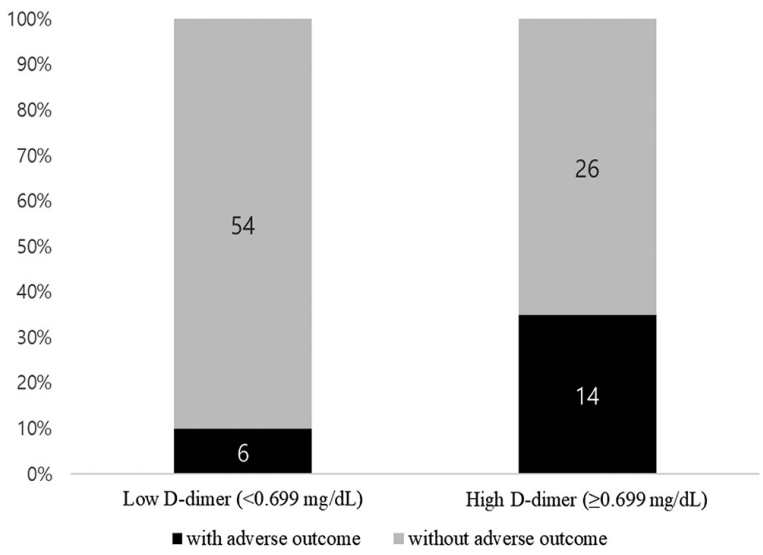

Fig. 1. Incidence of in-hospital adverse outcomes based on a cut-off D-dimer level of 0.699 mg/dL. Patients with antineutrophil cytoplasmic autoantibody-associated vasculitis (AAV) with D-dimer levels ≥0.699 mg/dL were at a higher risk of in-hospital adverse outcomes than those with D-dimer levels <0.699 mg/dL (35.0% *vs*. 10.0%, *p*=0.002).

Risk factors for in-hospital adverse outcomes among patients with AAV

We performed univariate and multivariate Cox proportional hazard regression analysis to evaluate the clinical parameters associated with adverse outcomes. Considering the half-life of D-dimer, we excluded the patients in whom D-dimer levels were measured 3 days after hospitalisation in this analysis. Multivariate analysis using the variables that showed a significant association with p-values <0.05 in the univariate analysis showed high D-dimer levels (HR 4.852 CI 1.320-17.833, *p*=0.017) and platelet counts (HR 0.541, 95% CI 0.341-0.920, *p*=0.022) were associated with adverse outcomes among patients with AAV (Table IV).

Kaplan-Meier analysis for adverse outcome of patients with AAV according to initial D-dimer levels

Patients with AAV with a high D-dimer level at hospitalisation had a higher 30-day adverse outcome rate than patients with a low D-dimer level (*p*=0.008) (Fig. 2).

Clinical and laboratory findings of patients with AAV who were admitted to the ICU or had in-hospital mortality

We further analysed the clinical data of nine patients who died during hospitalisation and fifteen patients who were admitted to the ICU (Suppl. Tables S1 and S2). All patients were hospitalised with vasculitis disease activity, and there was no evidence of infection or thromboembolism upon admission. The main clinical events leading to death or ICU admission were a need for ventilator support or shock. Seven of nine deceased patients had concomitant infection throughout hospitalisation, and cases in which infection was the main cause of death occurred 2 weeks after hospitalisation. All the patients who died within 2 weeks of hospitalisation were due to AAV exacerbation, and they all belonged to the high D-dimer group. Ten of the 15 patients admitted to the ICU required ventilator support due to haemoptysis or worsening of interstitial lung disease, while the remaining patients were admitted to the ICU due to shock and mental change. Twelve of 15 patients admitted to the ICU and 8 of the 9 deceased patients belonged to the high D-dimer group.

Drug-related effects on adverse outcomes

Corticosteroids and immunosuppressive drugs are indispensable for patients who are hospitalised owing to the worsening of vasculitis. These drugs have the potential to cause side effects, especially by increasing the risk of infection, which affect adverse

Table IV. Analysis of variables at the time of diagnosis for predicting adverse outcomes in AAV patients during the follow-up period using a Cox proportional hazards model (excluding patients in whom D-dimer levels were measured 3 days after hospitalisation).

Variables	Univariable			Multivariable		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)	1.010	0.979-1.043	0.533			
Male gender (n, (%))	1.454	0.576-3.694	0.431			
Disease duration	1.014	1.004-1.024	0.008	1.013	1.000-1.027	0.057
MPO-ANCA (or P-ANCA) positivity	0.373	0.112-1.240	0.107			
PR3-ANCA (or C-ANCA) positivity	1.839	0.532-6.353	0.335			
BVAS	1.006	0.919-1.103	0.890			
FFS ≥3	1.511	0.567-4.029	0.409			
Diabetes mellitus	1.275	0.410-3.965	0.674			
Hypertension	0.394	0.144-1.083	0.071			
Chronic kidney disease (stage 3–5)	0.679	0.220-2.097	0.501			
Dyslipidaemia	0.854	0.239-3.053	0.809			
Constitutional symptom	0.994	0.372-2.660	0.991			
Skin involvement	2.975	0.947-9.347	0.062			
Ear, nose, throat involvement	0.788	0.103-6.022	0.819			
Lung involvement	2.428	0.690-8.541	0.167			
Cardiovascular involvement	1.623	0.212-12.413	0.641			
Gastrointestinal involvement	2.646	0.744-9.416	0.133			
Renal involvement	1.107	0.317-3.865	0.873			
Nervous system involvement	0.904	0.294-2.784	0.861			
White blood cell count (/mm^3)	1.000	1.000-1.000	0.515			
Haemoglobin (g/dL)	1.043	0.846-1.286	0.692			
Platelet count (× 1,000/mm^3)	0.995	0.990-0.999	0.028	0.995	0.991-1.000	0.051
Blood urea nitrogen (mg/dL)	0.993	0.971-1.017	0.575			
Serum creatinine (mg/dL)	1.001	0.805-1.244	0.994			
Urine protein creatinine ratio	1.036	0.997-1.074	0.070			
Haematuria	0.616	0.390-0.973	0.038	0.541	0.341-0.920	0.022
ESR (mm/h)	0.997	0.983-1.012	0.734			
CRP (mg/L)	1.005	1.001-1.010	0.024	1.000	0.994-1.006	0.973
D-dimer ≥0.699 (mg/dL)	3.202	1.129-9.083	0.029	4.852	1.320-17.833	0.017

BVAS: Birmingham Vasculitis Activity Score; FFS: Five-Factor Score; CRP: C-reactive protein.

outcomes. There were 22 cases with concomitant infection over the treatment course, of which 11 cases had adverse outcomes. Patients who received glucocorticoid pulse therapy (≥500mg/day of methylprednisolone) had more concomitant infection than those who did not (42.1% *vs*. 17.5%, p=0.020), and patients with concomitant infection had more adverse outcomes than those without concomitant infection (50.0% *vs*. 10.4%, p<0.001). There was no other fatal drug-related effect on adverse outcomes.

Discussion

This study showed the potential of D-dimer as a prognostic marker in patients with AAV requiring hospitalisation. To the best of our knowledge, this is the first study to demonstrate the association of D-dimer level and poor hospitalisation outcomes in AAV. Based on our data, the suggested cut-off D-dimer level to predict adverse outcomes was 0.699 mg/dL, with an HR of 4.852.

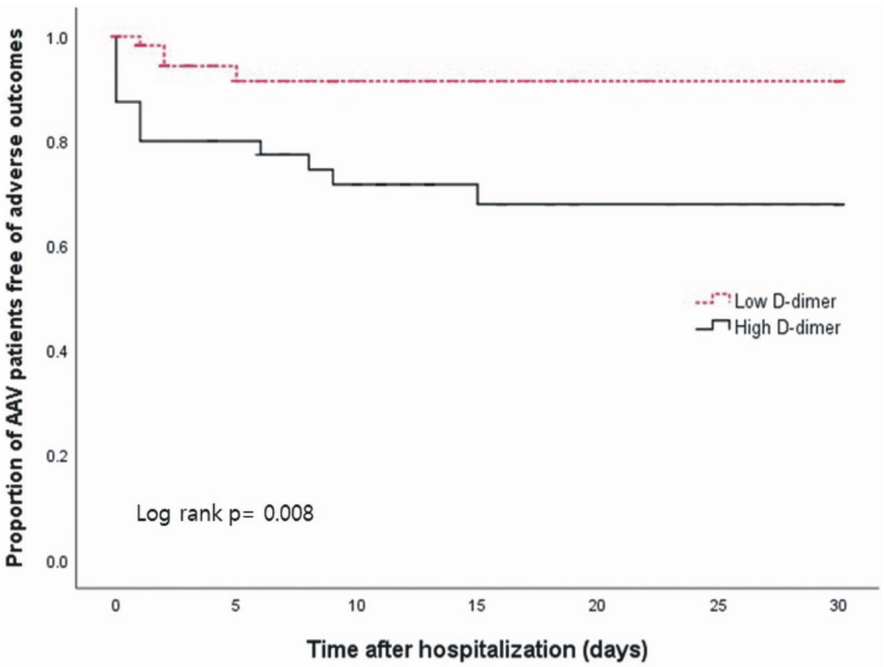

Fig. 2. Kaplan-Meier survival curve for in-hospital adverse outcomes stratified by the initial D-dimer levels. Red dotted line: patients with low D-dimer level (<0.699 mg/dL). Black dashed line: patients with a high D-dimer level (≥0.699 mg/dL). The incidence of in-hospital adverse outcomes was significantly higher among patients with high D-dimer levels than among those with low D-dimer levels (p=0.008).

AAV is a complex systemic disease involving multiple organs; thus, defining disease severity has been difficult. Commonly used tools, such as the BVAS, Physician Global Assessment, and FFS, may predict long-term outcomes, but their roles in predicting a short-term hospital course during acute exacerbations are limited. It is important to appropriately diagnose patients with an acute AAV flare because they could benefit from an escalated level of immunosuppression and more attentive care.

We found that D-dimer levels negatively correlated with serum albumin and haemoglobin and positively correlated with CRP, BVAS, and FFS. This finding is consistent with a previous report that D-dimer correlates with CRP in GPA patients (17). Given that serum albumin and haemoglobin levels decrease in acute inflammatory or critically ill conditions, and that CRP and BVAS are used as indicators of disease activity, these findings support our hypothesis that D-dimer levels correlate with disease activity at the time of hospitalisation.

Patients with adverse outcomes were older than those without in the present study. Previous studies demonstrated that elderly patients had more disease-related burden or treatment-related complications (18, 19). Therefore, there is a possibility that age affected adverse outcomes, such as the likelihood that the underlying disease burden for the patients with adverse outcomes was higher than that for those without adverse outcomes and the likelihood of more complications with immunosuppressive treatment. However, age was not a significant risk factor for adverse outcomes among patients with AAV in our multivariate Cox proportional hazard regression analysis.

Our results should be interpreted with caution because the D-dimer level can be elevated in various clinical settings such as thrombosis, infection, vasculitis, and others. Our study evaluated the D-dimer level at admission to predict poor hospital outcomes for AAV patients when no other conditions were observed. There is still a chance that subclinical infections that exists at hospitalisation and get worse after immunosuppressive therapy. Therefore, the potential confounding effect of infections on our result should be considered. Nonetheless, if the D-dimer level is elevated during or at hospitalisation on AAV patients, it is important to evaluate every possibility of causing endothelial dysfunction and vasculopathy rather than starting immunosuppressive therapy.

Fibrin clots are generally lysed by plasmin, subsequently yielding D-dimer (20, 21). D-dimer levels are elevated in various clinical conditions involving intravascular coagulation and fibrinolysis, or even in the absence of overt thromboses, such as post-surgery, malignancy, and pregnancy (22, 23). A recent study suggested that patients with GPA who had elevated D-dimer levels are in an active inflammatory status rather than venous thrombosis (17). Their study observed a mean D-dimer level of 0.652 mg/dL, which is similar to our cut-off D-dimer level for the high D-dimer group.

The exact mechanism underlying the elevation of D-dimer levels in patients with AAV remains unclear; however, this elevation is speculated to result from inflammation and NETosis, a cell death modality wherein invading microbes are entrapped through the release of decondensed DNA (24). ANCAs promote NETosis formation by binding to PR3 or MPO on the neutrophil surface (25, 26). NETosis can adhere to endothelial surfaces and cause tissue damage during neutrophil-induced inflammation (27). A study in patients with gastric cancer reported that D-dimer levels increase proportionately with an increase in NETosis (28). We hypothesise that D-dimer levels are associated with AAV activity, as AAV is characterised by the progression of vascular endothelial damage (29-31).

In our study, other commonly used parameters for vasculitis activity, such as BVAS, FFS, and CRP level, showed no correlation with adverse outcomes. Consistent with our result, Kimmoun *et al*. have reported similar data, that BVAS and FFS cannot predict in-ICU mortality (32). Several other biomarkers, such as CXC motif chemokine ligand 13, matrix metalloproteinase-3, and tissue inhibitor of metalloproteinases-1, have shown promising results in distinguishing active AAV from AAV remission (33). However, these markers are not yet clinically applicable.

This study had several limitations. First, there may have been a potential selection bias because this was a single-centre, retrospective, and cross-sectional study. Second, owing to the retrospective design of our study, various immunosuppressive regimens were applied. Third, there is a possibility that the underlying vasculitis burden differs between the high and the low D-dimer groups, which may affect the adverse outcomes. Fourth, because we do not have a separate validation group, the cut-off value of D-dimer as 0.699 mg/dL should be validated in other AAV cohorts in future studies. Finally, corroborating mechanistic data are needed to support D-dimer as a potential biomarker in hospitalised patients with AAV. Moreover, the exact mechanism underlying how D-dimer is elevated in patients with AAV and whether it is a mere result of systemic vascular inflammation or a part of disease pathogenesis remain unclear. The role of coagulation abnormality in vasculitis is an interesting topic that requires further research. Nevertheless, the strength of this study is that D-dimer levels can be considered a useful marker for predicting outcomes among patients with AAV, which can be easily assessed by a simple blood test at a low cost.

In conclusion, this study suggests that D-dimer levels of ≥0.699 mg/dL are an independent predictive biomarker for adverse outcomes among patients with AAV during their AAV flare, suggesting its role in guiding the care of patients with AAV.

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