D-Dimer As An Indicator of Vertebral Artery Dissection: A Case Control Study

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Abstract

Background

Vertebral artery dissection (VAD), which can possibly lead to stroke, presents various symptoms such as headache, neck pain, transient ischemic attacks, and vertigo. We evaluated the effect of D-dimer to distinguish VAD from benign diseases by retrospective single-center observational study.

Methods

All VAD cases received in the emergency department between January 2013 and June 2020 were reviewed. Comparing those cases to vertigo with benign etiologies, the correlation between VAD and D-dimer was analyzed. Using stepwise multivariate logistic regression, possible symptoms to suspect VAD were also determined from physical findings and some laboratory data, including D-dimer.

Results

Eleven patients were included in the VAD group, and 59 patients were enrolled in the control (benign vertigo [BV]) group. The most common symptom in VAD patients was hemiplegia (N = 7, 63.6%) and cranial neuropathy (N = 7, 63.6%), followed by classic occipital or posterior neck pain (N = 4, 36.4%), gait ataxia (N = 3, 27.3%), and confusion (N = 1, 9.1%). Two patients (18.2%) were free from any symptoms except vertigo. D-dimer was not significantly different between the two groups at the positive cutoff value of 500 ng/mL ($p = 1$). By stepwise selection, age (odds ratio (OR): 0.92, [0.87–0.98], $p < 0.01$) and systolic blood pressure (sBP; OR: 1.06 [1.02–1.10], $p < 0.01$) were selected in the diagnostic model. In combination, age under 60 and sBP over 160 mmHg yielded 63.6% sensitivity, 98.3% specificity, and 37.5 positive likelihood ratio.

Conclusions

In our study, D-dimer was not found to be an effective indicator of VAD. By contrast, disproportionate hypertension (high blood pressure in young patients) can be a key factor to suspect VAD. Future studies with larger sample sizes are warranted.

Background

Vertebral artery dissection (VAD) is estimated to occur in 0.97 per 100,000 individuals annually.[1] This relatively rare disease presents various clinical symptoms such as headache, neck pain, transient ischemic attacks, vertigo, and Horner syndrome.[2] Since none of the symptoms above are necessary for a diagnosis, this disease is notorious for its tendency to be overlooked. Some cases do not even present cerebral ischemic symptoms, while others are entirely asymptomatic.[3, 4] Despite its insufficient clinical

detection, this disease can possibly lead to critical consequences such as subarachnoid hemorrhage (SAH).[5]

VAD diagnosis is confirmed by neuroimaging.[6] Although computed tomography (CT) and magnetic resonance imaging (MRI) are useful in patients with a high suspicion for VAD, factors that can potentially raise suspicion other than clinical features have not been established. Distinguishing the potentially lethal VAD from benign diseases is important. Therefore, less invasive and more approachable methods to determine VAD are warranted.

D-dimer is one of the major fibrin degradation products widely known as a highly sensitive biomarker used to detect coagulating system abnormalities,[7, 8, 9] such as deep venous thrombosis (DVT), pulmonary embolism (PE), and/or disseminated intravascular coagulation (DIC). Furthermore, D-dimer testing is also becoming an important indicator in effectively ruling out aortic dissection.[10, 11] However, the usefulness of D-dimer in detecting VAD has not been explored.

A single-center retrospective observational study was conducted (1) to investigate if D-dimer is useful for VAD diagnosis and (2) to detect other signs to raise clinical suspicion for VAD.

Methods

Patient inclusion

We performed a hospital-based, retrospective, observational, case-control study in a tertiary emergency center, the University of Tsukuba Hospital in Japan. The study was conducted in accordance with the regulations of Institutional Review Board and the protocol was approved with the following reference number: R03-006.

We collected medical information on the patients who visited the emergency department (ED) presenting vertigo between January 2013 and June 2020. Since CT or MRI is necessary for confirmed diagnoses, the patients without neuroimaging records were excluded. Patients confirmed with VAD comprised the study (VAD) group. Patients without vascular etiologies or those who were discharged were excluded, since cases that did not require admission were deemed not severe enough to be virtually compared with VAD. The remaining patients who presented benign vertigo and required hospitalization were included as the control group.

Data collection

Parameters such as age, sex, hypertension (HT), diabetes mellitus (DM), dyslipidemia, and anticoagulation medication were extracted from the patients' medical records on admission. The presence of HT, DM, dyslipidemia, and anticoagulation were determined by two factors: (1) if they were on medication to treat each condition, and (2) if they were discharged with registration of each condition. Vital signs on admission including systolic blood pressure (sBP)[12] and heart rate (HR), were extracted, as well as the following laboratory data: potassium (K), creatinine (CRE), C-reactive protein (CRP), blood

glucose (BG), leukocyte count (WBC), hemoglobin (Hb), thrombocyte count (Plt), activated partial thromboplastin time (APTT), prothrombin time/international normalized ratio (PT-INR), and D-dimer. Complete blood count, CRP, APTT, and PT-INR were measured because a previous study indicated the possibility of the correlation between cervical artery dissection and a hypercoagulable state and simultaneous inflammatory condition.[13] Likewise, based on an earlier study demonstrating a possible association between SAH and K and BG changes as a physiologic response, those variables were also included.[14]

Statistical analysis

Differences in baseline data between the two groups were assessed by Fisher's exact test for categorical variables and by Student's *t*-test for continuous variables.

The correlation between VAD and D-dimer was assessed as a nonparametric variable using the Mann–Whitney U test and as a categorical variable by Fisher's exact test with a positive cutoff of 500 ng/mL.[10, 11]

In order to detect the contribution of each variable to VAD and thus minimizing statistical confounding factors, multivariate logistic regression was performed with the response variate as the presence of VAD and the explanatory variates as age, sBP, HR, K, CRE, CRP, BG, WBC, Hb, Plt, APTT, PT-INR, and D-dimer. Stepwise selection was performed to establish a diagnostic model, managing large amount of potential predictor variables within a small sample size.[15] Missing values were filled in by performing multiple imputation by chained equation (MICE) 100 times. Using backward stepwise selection based on the Bayesian information criterion, the variates selected over 50 times out of 100 multiple imputations were included in the models.[16] Regarding the selected models, analytical results were integrated by Rubin's rules, and the odds ratio (OR) of each variate was estimated. The mean c-statistic was calculated to evaluate model prediction performance.

All analyses were performed using R ver. 4.0.3 (R Core Team, 2020). The MICE package ver. 3.11[17] was used in multiple imputation. A two-tailed *p*-value under 0.05 was considered to be statistically significant.

Results

Of the 72,038 patients who visited the ED, 810 presented with vertigo. Of these, 260 cases were excluded because they did not undergo CT or MRI. Of the remaining 550 patients, 23 patients demonstrated vascular etiologies including seven SAH, 1 intracranial hemorrhage, 3 cerebellar infarctions without vertebral lesions, and 11 VAD. The other 527 patients were regarded as benign. A total of 468 patients were excluded because they were discharged from the ED without admission. The remaining 59 patients were defined as the control or benign vertigo (BV) group. Altogether, 70 patients were identified to be analyzed for this study (Fig. 1).

The baseline characteristics of both groups are shown in Table 1. Patients with VAD were significantly younger than those with BV (53 ± 13 years vs 67 ± 15 years, $p < 0.01$). No significant difference was

observed in sex, HT, DM, dyslipidemia, and anticoagulant medication use.

Table 1
Baseline characteristics of study subjects.

Variables	VAD	BV	*p*-value
n	11	59	
Age, years (M ± SD)	53 ± 13	67 ± 15	< 0.01
Sex, female [*n* (%)]	4 (36.4)	33 (56.0)	0.33
HT, *n* (%)	3 (27.3)	25 (42.4)	0.51
DM, *n* (%)	0 (0)	7 (11.9)	0.59
Dyslipidemia, *n* (%)	0 (0)	6 (10.2)	0.58
Anticoagulation use, *n* (%)	0 (0)	7 (11.9)	0.59
VAD group was significantly younger than BV group. Other baseline characteristics did not provide significant differences.			
M, mean; *SD*, standard deviation; *VAD*, vertebral artery dissection; *BV*, benign vertigo; *HT*, hypertension; *DM*, diabetes mellitus.			

Within the VAD group, seven patients (63.6%) presented with unilateral limb numbness or paralysis, seven patients (63.6%) with cranial neuropathy (such as unilateral myosis, diplopia, dysphagia, dysarthria, or glossoplegia), four patients (36.4%) with occipital or posterior neck pain, three patients (27.3%) with gait ataxia, and one patient (9.1%) with confusion. All of them were sudden onset. Some of them indicated a minor injury or trivial event prior to the ED visits (Table 2). For example, one patient was hit by a toy thrown by her child on the left posterior of her neck (lesioned part) two days before the visit. Another patient hit the posterior of his head on his bed two months before. Three other patients had been feeling fatigue and heaviness on the posterior of their necks from one week to two months before the onset. One of them had acute worsening of a headache after he caught a cold three days before. Other circumstances of the onsets were varied. One patient felt numbness while she was eating. Another felt nausea and right limb paralysis while she was baking a cake. Another felt vertigo while she was typing on a computer.

Table 2
Series of each patient history

Pt.	Trigger events	Circumstances at onset	Confusion	Hemiplegia	Gait ataxia	Cranial neuropathy	Location of the pain
1.	Trauma to the head (2 days prior)	Restroom	-	-	-	-	Left posterior, neck
2.	None	Eating	-	+	-	+	None
3.	Heaviness in neck (1 week prior)	Sitting	-	+	+	+	None
4.	None	Cooking	-	+	-	+	None
5.	Common cold (3 days prior)	Coughing	-	+	-	+	Right posterior, neck
6.	Elevation of right arm	Elevating her right arm	-	+	-	-	Right posterior, neck
7.	Heaviness in neck (1 week prior)	Typing on a computer	-	-	+	+	None
8.	Head trauma (2 months prior)	Walking	-	-	+	-	None
9.	None	Walking	-	+	-	+	Posterior headache
10.	Posterior right headache (1 month prior)	Watching TV	+	+	-	+	None
11.	None	Sitting	-	-	-	-	None
All of the possible triggering events, circumstances on the onsets, neurological symptoms including level depression of consciousness, limbs paralysis, cranial neuropathy, and cerebellar dysfunction, and the location on the pain are demonstrated.							
Seven (63.6%) patients experienced possible triggering events before the onsets. The longest latent period was two months.							

Pt.	Trigger events	Circumstances at onset	Confusion	Hemiplegia	Gait ataxia	Cranial neuropathy	Location of the pain
One (9.1%) patient presented consciousness level decline.							
Seven (63.6%) patients presented right or left hemiplegia.							
Three (27.3%) patients presented gait ataxia.							
Seven (63.6%) patients presented cranial neuropathy including anisocoria, diplopia, facial palsy, dysphagia, dysarthria, and glossoplegia.							
Four (36.4%) patients presented headaches or posterior neck pains.							
Pt. Patients							

D-dimer as a continuous variable did not vary significantly between the two groups ($p = 0.84$; Fig. 2). Likewise, no significant difference was observed between the two groups when 500 ng/mL was set as a positive cutoff value. (11 positives and 0 negatives in the VAD group vs 55 positives and 4 negatives in the BV group; $p = 1$).

Using multivariate logistic regression with backward stepwise selection (Table 3), two variables were selected into the diagnostic model; age (OR = 0.92; 95% confidence interval [CI] = 0.87–0.98; $p = 0.005$) and sBP (OR = 1.06; 95% CI = 1.02–1.10; $p = 0.002$). The mean c-statistic of the selected models was 0.86. For the selected variables, we performed calculations of sensitivities and specificities to establish diagnostic cutoffs. In age, sensitivity plus specificity maximized with 60 years as the cutoff value (0.636 + 0.746 = 1.382). In sBP, sensitivity plus specificity maximized with 160 mmHg as a cutoff value (0.818 + 0.881 = 1.699). In combination, age under 60 and sBP over 160 mmHg provided 63.6% of sensitivity and 98.3% of specificity, indicating 37.5 of positive likelihood ratio.

Table 3
Results of backward stepwise selection

Variates	OR	*p*-value
Age (95% CI)	0.92 (0.87–0.98)	< 0.01
sBP (95% CI)	1.06 (1.02–.10)	< 0.01
Out of the 13 variables, 2 variables were selected in the diagnostic model using stepwise selection. Both of the selected variables, age and sBP provided significant differences between VAD group and BV group.		
sBP, systolic blood pressure; *OR*, odds ratio; *CI*, confidence interval, *VAD*, vertebral artery dissection; *BV*, benign vertigo.		

Discussion

In the present study, D-dimer was found to be a nonsignificant clinical indicator for detecting VAD. These findings are helpful in clinical practice because decisions based on laboratory data can directly affect outcomes.

From a pathophysiological viewpoint and contrarily to aortic dissection, in which degeneration of the aortic media is followed by an intimal tear, VAD is thought to occur as a subintimal dissection causing an intramural hematoma and leading to cerebral hypoperfusion,[18] or as a subadventitial dissection creating an extraluminal pouch and leading to localized symptoms from the compression of adjacent nerves and their feeding vessels.[19] Although both aortic dissection and VAD feature the separation of arterial wall layers,[20, 21] these mechanisms are not identical. This difference in pathogenesis can explain why D-dimer might not be useful in indicating VAD.

Another possible hypothesis is that D-dimer might reflect the influence of systemic circulation, which is determined by the size of the vessels and the length of exposure. In arterial etiology, for instance, aortic size is strongly correlated with dissection occurrence. Paruchuri et al.[22] reported a mean ascending aortic diameter of 3.2 cm in non-diseased adults. Furthermore, more than 95% of the non-diseased population demonstrated an ascending aortic diameter under 3.9 cm, whereas nearly 90% of patients with aortic dissection demonstrated an ascending aortic diameter over 4.0 cm. Small arteries such as the vertebral artery (mean diameter 3.6–4.5 mm)[23] or superior mesenteric artery (mean diameter 6.2–8.0 mm)[24] might be too small to affect the coagulation system acutely even when they are dissected. By contrast, in venous etiology, DVT might be chronic enough to be reflected in laboratory tests. Although the results of this study could not establish an association between D-dimer and VAD, it was also conducted with a small sampling size, which are similar circumstances to those in previous studies on the superior mesenteric artery or cervical artery dissections.[25, 26, 27] Importantly, however, unelevated D-dimer levels do not exclude the possibility of VAD. Future studies with larger statistical power are therefore warranted.

On the other hand, the combination of a younger age and elevated blood pressure could raise the suspicion for VAD, which is known to have a high incidence among young adults. However, other clinical features vary from case to case. While some trigger events such as sports, cervical manipulation, trauma, intense sneezing, or coughing are indicated as clues,[28, 29] not every case presents such evident histories.[4] In the present study, while all of the included patients with VAD presented with vertigo, other clinical features varied widely. Some trigger events were observed prior to the onset, but these involved less than half of the included patients. The time period between the events and the onsets also varied widely from two days to two months. Asking patients who are suffering of vertigo and heavy nausea about their headaches two months prior does not seem to be an effective way of narrowing down differential diagnoses in the ED. Neurological symptoms were the second most common presentation in our study, and yet, two patients were free from any neurological symptoms. The specific characteristics or symptoms that distinctly indicate VAD thus remain unelucidated.[2, 30]

Nevertheless, our study demonstrated the positive relation between blood pressure and VAD. In general, high blood pressure is unsurprising in stroke patients. Although the presence of HT was not significantly

different between the two groups, HT is generally a strong risk factor for ischemic stroke.[31] The physiologic response that maintains cerebral perfusion also results in increased blood pressure.[32] However, the prevalence of HT is generally lower in young adults.[33] Thus, disproportionate hypertension is unusual enough to raise suspicion for VAD. Although our sample size was not sufficient enough to guarantee the generalizability, the positive likelihood ratio (LR) of the combined criteria of age under 60 years and sBP over 160 mmHg was remarkable at 37.5. We believe in the simplicity of this criterion and the substantiality of the positive LR in clinical practice carries some significance worthy of further investigation. Thus, if a young patient visited an ED and presented with sudden-onset vertigo and/or headache with disproportionate hypertension, the patient should be endorsed for MRI even without any neurological symptoms or triggering events.

This study has several limitations. Firstly, this study was performed based on a single-center retrospective observational design. Although we reviewed eight years' worth of medical records, only a small sample size could be obtained. Some of the parameters were possibly mis-analyzed as nonsignificant even with a fair prediction performance of the selected diagnostic model. Secondly, The proportion of the symptoms in our data varied with those in other studies.[1, 2] For example, according to the study by Lee VH et al, the most frequent initial symptom of cervical artery dissection, which includes both internal carotid artery dissection and vertebral artery dissection, was head and/or neck pain (80%). By contrast, in our study, as low as 36% of the included patients presented such symptoms. This discrepancy may imply the insufficient external validity of our findings. Thirdly, due to the retrospective study design, the data we could use were only extracted from medical records, which possibly made us miss important data points. Furthermore, many of the variables we used were unavailable from the records. Even with MICE, our results were not definitely conclusive or generalizable. Since rare diseases like VAD tend to be difficult to evaluate within one institute, multi-center studies with larger sample sizes are warranted in the future.

In conclusion, our findings did not demonstrate the usefulness of D-dimer for VAD diagnosis. Physicians should, however, keep in mind that unelevated D-dimer levels do not exclude the possibility of VAD. By contrast, disproportionate hypertension could possibly indicate VAD. Vital signs should be closely considered with the presenting symptoms. Future studies with larger-scale and multi-center designs should be undertaken to attain conclusive findings on the relationship between D-dimer and VAD, as well as to obtain more in-depth information on the mechanism of this disease.

Conclusions

D-dimer was not proven to be an effective indicator to suspect VAD. Further investigations with larger sample sizes are warranted.

List Of Abbreviations

APTT, Activated partial thromboplastin time

BG, Blood glucose

CI, Confidence interval

CRP, C-reactive protein

CT, Computed tomography

DIC, Disseminated intravascular coagulation

DM, Diabetes mellitus

DVT, Deep venous thrombosis

ED, Emergency department

HR, Heart rate

LR, Likelihood ratio

MICE, Multiple imputation by chained equation

MRI, Magnetic resonance imaging

PE, Pulmonary embolism

Declarations

Ethics approval and consent to participate

This study was comprehensively explained on our website and announced including opt-out opportunities. We also obtained verbal consent from all patients regarding the possibility of participating in retrospective clinical studies in which no personal information can be indentified. Our Institutional Review Board (Tsukuba Clinical Research & Development Organization: T-CReDO) approved this study with the reference number: R03-006.

Consent for publication

Not applicable

Availability of data and materials

The dataset supporting the conclusions of this article is attached as its additional file.

Competing interests

Not applicable

Funding

Not applicable

Authors' contributions

AW designed the study, carried out sample collection, analyzed data, and wrote the manuscript. YE, AM, NS, and YI participated in designing study. HI, JN, TK, TS, TH, YM, and YK participated in sample collection. KM supported statistical analysis. All authors read and approved the final manuscript.

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Not applicable

Authors' information

Not applicable

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Figures

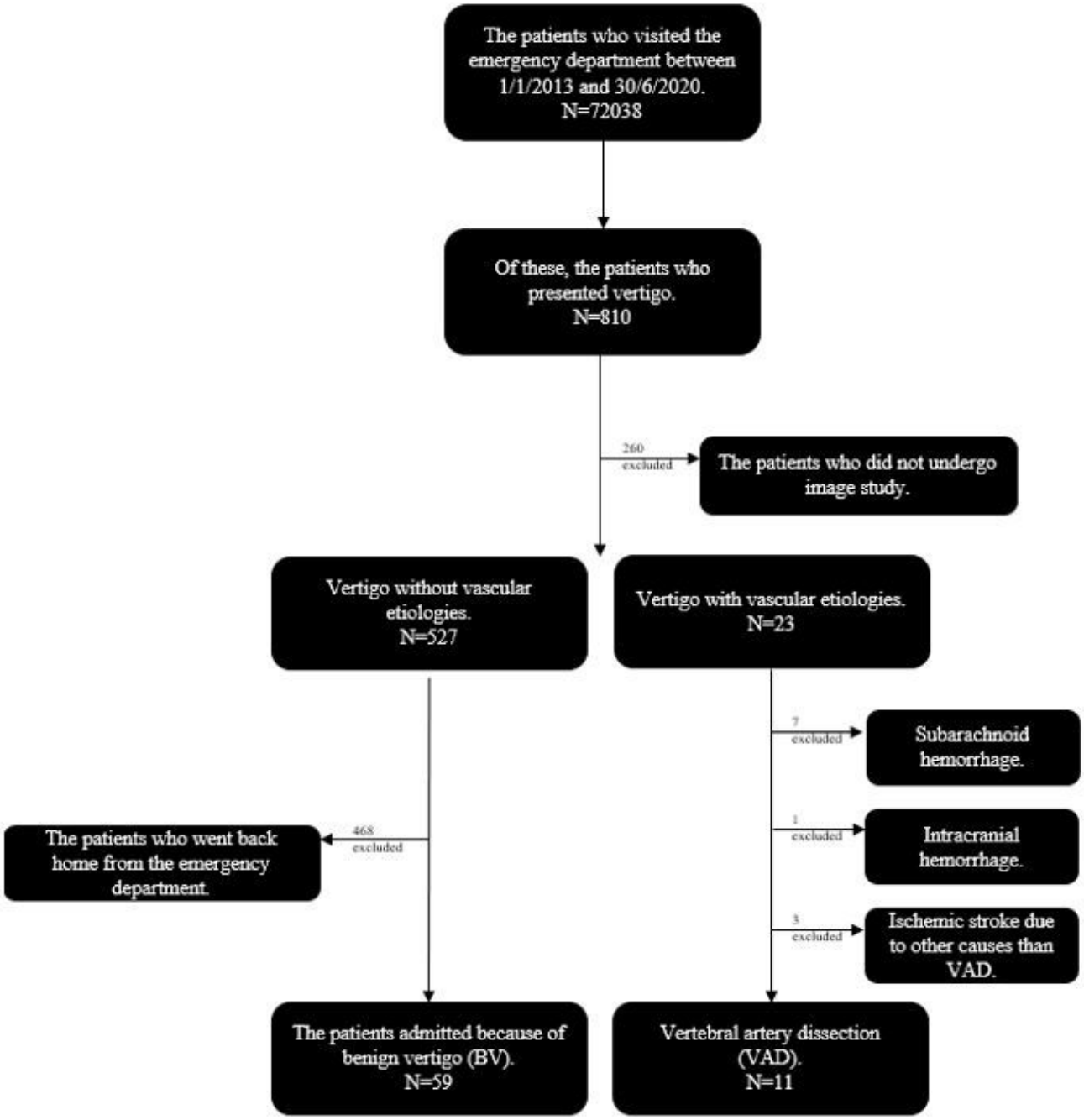

Figure 1

Patient inclusion flowchart. Of the total 72,038 patients who visited the ED between January 2013 and June 2020, 810 were presenting vertigo. Those with VAD were compared to those without vascular etiologies but required admission. Eventually, 70 patients were included.

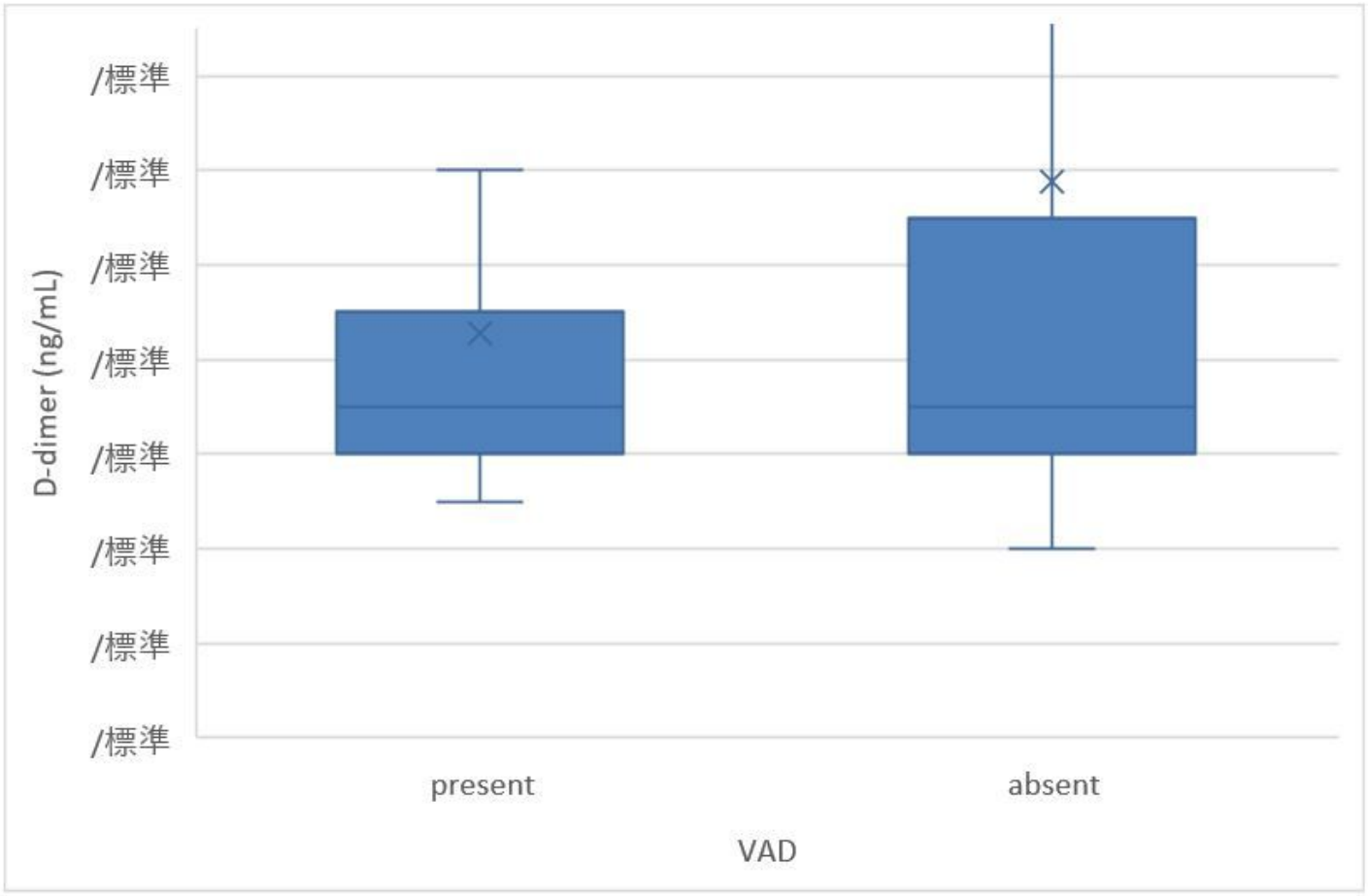

Figure 2

Box-whisker plot of D-dimer (ng/mL) based upon the presence of VAD. As a continuous variable, D-dimer did not provide a significant difference between the two groups.