



Research Article

D-dimer as an Indicator of Vertebral Artery Dissection: an observational study

Atsuyuki Watanabe¹, Hiroshi Ito¹, Kazushi Maruo², Junzo Nakao¹, Tetsuya Hoshino¹, Yuki Enomoto¹, Aiki Marushima¹, Nobutake Shimojo¹, Yoshiaki Inoue^{1*}

¹Department of Emergency and Critical Care Medicine, University of Tsukuba Hospital, Japan

²Department of Biostatistics, Faculty of Medicine, University of Tsukuba, Japan

***Corresponding author:** Yoshiaki Inoue, Department of Emergency and Critical Care Medicine, University of Tsukuba Hospital 2-1-1 Amakubo, Tsukuba, Ibaraki 305-8576, Japan.

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Abstract

Vertebral artery dissection (VAD) diagnoses are sometimes challenging. Associations between VAD and D-dimer has not yet been explored. We conducted a single-center retrospective study to evaluate the usefulness of D-dimer in VAD diagnoses.

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 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 vertigo (N=11, 100%), followed by hemiplegia (N = 7, 63%) and cranial neuropathy (N = 7, 63%). Two patients (18%) 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

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.

Keywords: Cervical artery dissection; D-dimer; Disproportionate hypertension; Stroke; Vertebral artery dissection

Introduction

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 specific to VAD, this disease is often overlooked. Some cases are sometimes 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 helpful 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 [7-9]. such as deep venous thrombosis (DVT), pulmonary embolism (PE), and disseminated intravascular coagulation (DIC). Furthermore, D-dimer testing is also becoming an essential indicator in effectively ruling out aortic dissection [10,11]. However, the usefulness of D-dimer in detecting VAD has not been explored.

This study aimed to investigate if D-dimer is useful for VAD diagnosis and to detect other signs to raise clinical suspicion for VAD.

Methods

Patient inclusion

We performed a hospital-based, retrospective, observational study in a tertiary emergency center, the University of Tsukuba Hospital in Japan. The study was conducted in accordance with the institutional regulations. The protocol was approved by the Institutional Review Board (Approval No: 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. All of the taken imaging studies were screened by emergency physicians, neurosurgeons, and diagnostic radiologists in charge of each case. The final assessments on the medical records were extracted. Among the patients without vascular etiologies,

we excluded the patients who were discharged from the ED. Patients confirmed with VAD comprised the study (VAD) group. Each patient's diagnosis was also guaranteed by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) code I-72.6 (aneurysm and dissection of vertebral artery) on discharge records. The remaining hospitalized patients who presented no vascular etiologies in imaging studies were included as the control (benign vertigo: BV) group.

Data collection

Patient medical records were manually reviewed to obtain the following variables: 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 the registration of each condition. Vital signs at the ED, 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 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].

We performed a multivariate logistic regression with variables determined by stepwise selection. Missing values were filled in using multiple imputations by chained equation (MICE) 100 times. The variates selected over 50 times out of 100 multiple imputations were included in the diagnostic models [15]. Regarding the selected models, analytical results were integrated by Rubin's rules, and each variate's odds ratio (OR) 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 was used in multiple imputations [16]. A two-tailed p-value under 0.05 was considered to be statistically significant.

Results

Of the 72,038 patients who visited the ED during the study period, 810 presented with vertigo. We excluded 260 cases without records of CT or MRI. Of the remaining 550 patients, 23 patients demonstrated vascular etiologies, including 7 SAH, 1 intracranial hemorrhage, 3 cerebellar infarctions without vertebral lesions, and 11 VAD. All of the VAD diagnoses were confirmed by MRI findings. Typical imaging characteristics were string sign, crescent sign, and tapered occlusion shown in (Figure 1) The other 527 patients were regarded as benign. After removing 468 non-hospitalized patients, 59 patients were defined as the control group (benign vertigo [BV]). Altogether, 70 patients were included in the analysis (Figure 2).

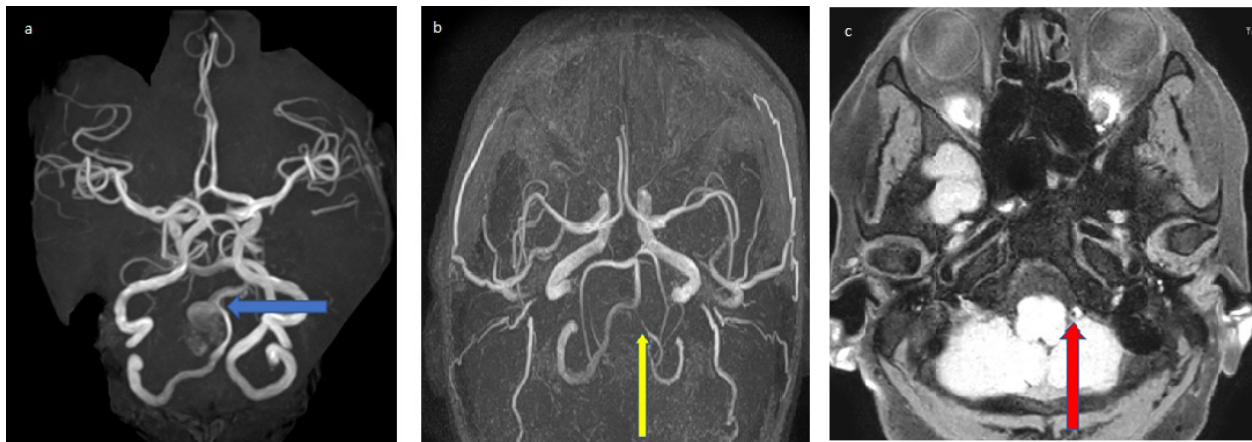


Figure 1: Typical imaging of vertebral artery dissection; (a) (blue arrow) shows the unruptured vertebral artery dissecting aneurysm and its distal narrowing (string sign); (b) (yellow arrow) shows fusiform dilation and the following narrowing of the left vertebral artery (tapered stenosis); (c) (red arrow) shows hypointense arterial lumen surrounded by hyperintense intramural hematoma in blood block T1-weighted MRI (crescent sign).

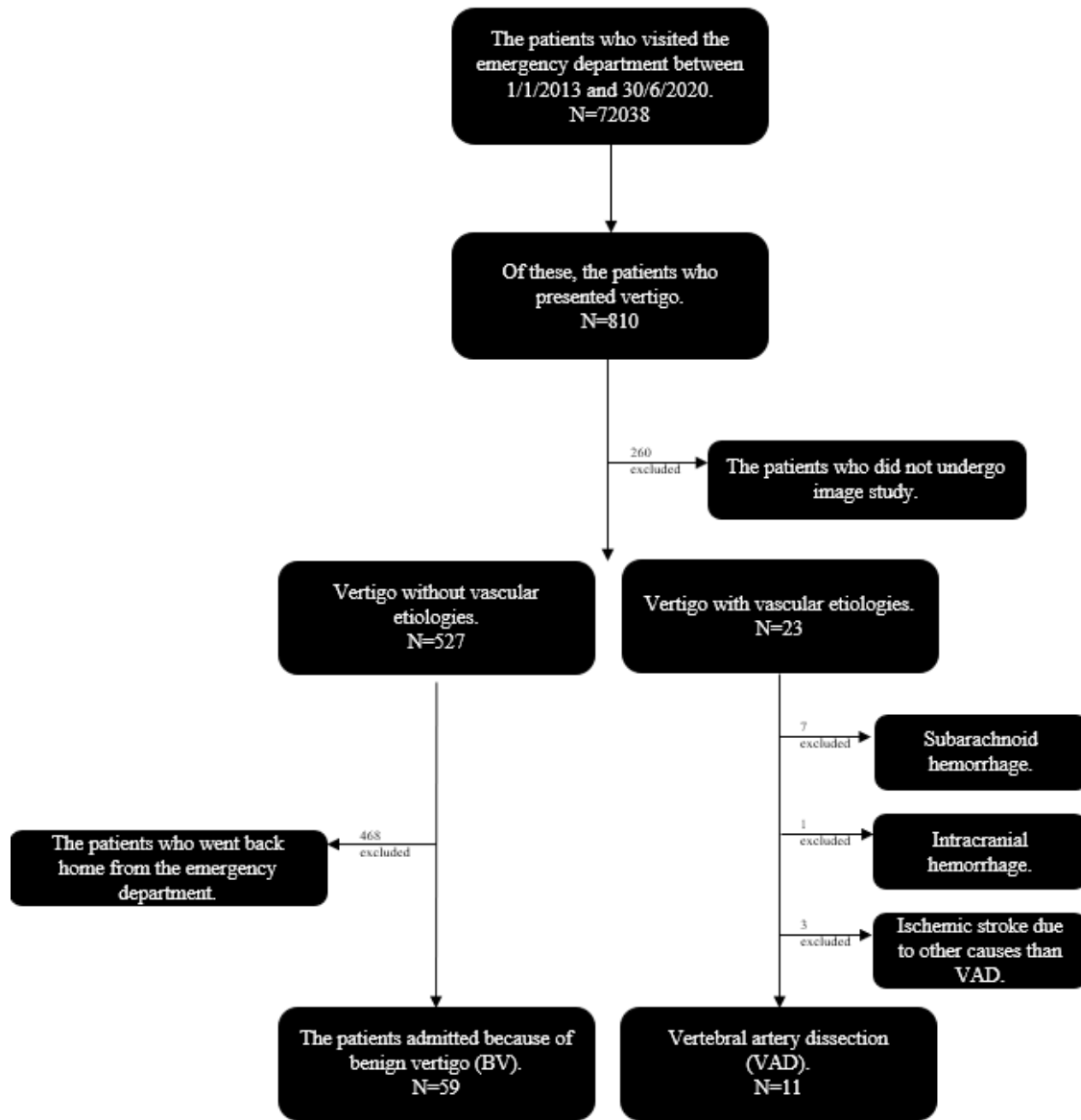


Figure 2: Flow diagram of patient inclusion.

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.

Variables	VAD	BV	p-value
<i>n</i>	11	59	
Age, years (M [SD])	53 (13)	67 (15)	< 0.01
Sex, female (<i>n</i> [%])	4 (36)	33 (56)	0.33
HT, <i>n</i> (%)	3 (27)	25 (42)	0.51
DM, <i>n</i> (%)	0 (0)	7 (12)	0.59
Dyslipidemia, <i>n</i> (%)	0 (0)	6 (10)	0.58
Anticoagulation use, <i>n</i> (%)	0 (0)	7 (12)	0.59

Table 1: Baseline characteristics of the two groups.

Within the VAD group, 11 patients (100 %) presented with vertigo, seven patients (63 %) presented with unilateral limb numbness or paralysis, seven patients (63 %) with cranial neuropathy (e.g unilateral myosis, diplopia, dysphagia, dysarthria, or glossoplegia), four patients (36 %) with occipital or posterior neck pain, three patients (27 %) with gait ataxia, and one patient (9.1%) with confusion. All of them were sudden-onset. Some of them indicated minor injury or trivial events 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 struck the back of his head on a bed two months before. Three other patients had been feeling fatigued and heavy 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. No significant difference in D-dimer was observed between the two groups either as a continuous variable ($p = 0.84$; Figure 3) or 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; $p = 1$).

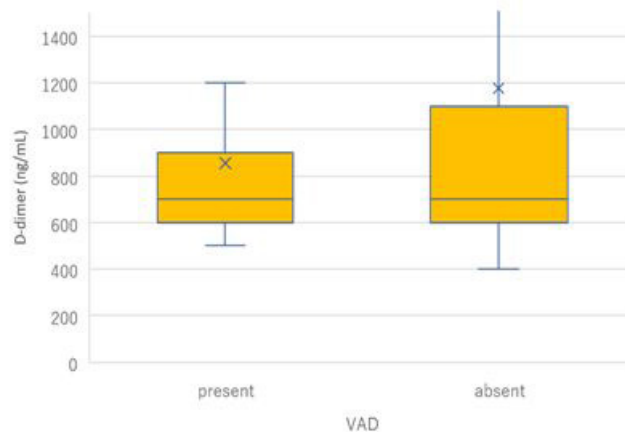


Figure 3: Box-whisker plot of D-dimer (ng/mL) of the two groups.

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

Table 2: Clinical features of each case.

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). Both of the selected variables provided statistically significant differences. 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. As for age, sensitivity plus specificity maximized with 60 years as the cutoff value (0.636 + 0.746 = 1.382) whereas that of sBP maximized with 160 mmHg as a cutoff value (0.818 + 0.881 = 1.699). In combination, ages under 60 and sBP over 160 mmHg provided 63.6 % of sensitivity and 98.3 % of specificity, indicating 37.5 of positive likelihood ratio.

Variates	OR	p-value
Age (95 % CI)	0.92 (0.87-0.98)	0.005
sBP (95 % CI)	1.06 (1.02-.10)	0.002

Table 3: Selected variables by stepwise selection and each effect size.

Discussion

Our results indicate that D-dimer measurement may not be helpful in the diagnosis of VAD, unlike in the diagnosis of aortic dissection. By contrast, age combined with sBP may raise suspicion for VAD.

Previous studies investigating the usefulness of D-dimer have been promising in diagnosing coagulopathy. According to several prospective studies, D-dimer lower than 500 ng/mL can reliably rule out acute aortic dissection [10,11]. On the contrary, the

association between D-dimer and VAD has scarcely been reported. To our knowledge, this is the first report on the association between D-dimer and VAD.

From a pathophysiological viewpoint, the mechanisms of aortic dissection and VAD are not identical, although both feature the separation of arterial wall layers [17,18]. The degeneration of the tunica media causes aortic dissection. However, VAD occurs as a result of sub-intimal or sub-adventitial tears. These tears are followed by an intramural hematoma and subsequent cerebral hypoperfusion [19] or an extraluminal pouch and subsequent

compression of adjacent nerves and their feeding vessels [20]. The size of dissected vessels can be another critical factor. A database analysis reported the significant differences between dissected and non-diseased aortic diameters [21]. According to retrospective studies mean diameter of vertebral arteries is smaller than that of superior mesenteric arteries [23,24] D-dimer failed to provide significant differences [24]. These differences in pathogenesis and size can explain why D-dimer may not be practical in indicating VAD.

Another clinical implication of this study is the discovery of disproportionate hypertension as a potential clue to suspect VAD. Previously, several studies have revealed triggering events of VAD, including sports, cervical manipulation, trauma, intense sneezing, or coughing [25,26]. Headache and neurological symptoms were also reported as common symptoms [3,4]. However, those were neither sensitive nor specific. In this study, 18 % of the participants presented no such findings. Another well-known risk factor for ischemic stroke is hypertension [27]. which is not specific as well. Thus, the sensitivity and specificity provided by the combination of the younger age and higher blood pressure in this study were noticeable. Because hypertension is more prevalent in the older population [28]. disproportionate hypertension can be unusual enough to raise suspicion for VAD. Therefore, if a young patient visited an ED and presented with sudden-onset vertigo and headache with disproportionate hypertension, the patient should be recommended for MRI even without any neurological symptoms or triggering events.

Several limitations of this study should be acknowledged. Firstly, although we collected eight years' worth of medical records, only a small sample size could be obtained. Some of the parameters were possibly mis-analyzed as non-significant even with a fair prediction performance of the selected diagnostic model. Secondly, since the study was conducted in a tertiary institute, the selected patients may not represent the general population. Thirdly, due to the retrospective study design, many of the variables were unavailable from the records. The use of MICE method does not guarantee the generalizability of our results. Since rare diseases like VAD tend to be challenging to evaluate within one institute, multi-center studies with larger sample sizes are warranted in the future.

Conclusions

D-dimer was not proven to be an effective indicator to suspect VAD. 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 always be attended to, as well as 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.

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N/A

Disclosure

Approval of the research protocol: The protocol was approved by Tsukuba Clinical Research & Development Organization (Approval No: R03-006).

Informed Consent: The requirement for informed consent was waived.

Registry and the Registration No. of the study: N/A

Animal Studies: N/A

Conflict of interest: No

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