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Original article

D-dimer assay not adequate for spontaneous intracranial hemorrhage screening

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Background: Patients with signs/symptoms of spontaneous intracranial hemorrhage (SICH) in the emergency department (ED) generally undergo computed tomography (CT) scanning.
Objective: To assess whether D-dimer assay alone at ED admission can be used for screening non-traumatic patients with suspected ICH who do not have new onset of neurological deficits to reduce the number of CT scans.
Methods: The study included 90 non-traumatic patients who were admitted to the ED and had signs/symptoms suggestive of SICH but did not have new neurological deficits. All patients underwent non-contrast CT within 30 minutes. Three patients also underwent lumbar puncture for a definitive diagnosis. Blood D-dimer levels were measured from venous blood samples obtained in the ED. All patients were followed up for one year. The diagnosis at 3 months follow-up was used to determine whether CT was helpful.
Results: CT was not helpful for 60 patients and was necessary for 30 patients. Multivariate analysis showed that dizziness/vertigo, systolic blood pressure >120 mmHg, and positive D-dimer assay (>500 ng/ml) were significantly related to the need for CT. The results of multivariate analysis were used to perform area under the curve analysis to provide data on sensitivity, specificity, positive predictive value, and negative predictive value for these three independent factors that affect the need for CT examination. Further analysis showed that all seven patients with subarachnoid hemorrhage had a positive D-dimer assay and their median D-dimer level was significantly higher than that of patients with intracerebral hemorrhage or stroke.
Conclusions: D-dimer assay alone is inadequate in the ED for screening non-traumatic patients with suspected SICH who do not have new onset of neurological deficits to reduce the number of CT scans.

Keywords: Computed tomography, D-dimer assay, fibrinolysis, spontaneous intracranial hemorrhage, subarachnoid hemorrhage

Hemorrhagic cerebral vascular accidents comprise up to 20% of all cerebral vascular accidents [1]. One of the more common reasons for ordering computed tomography (CT) scans in the emergency department (ED) is suspicion of intracranial hemorrhage (ICH) because failure to diagnose ICH has catastrophic consequences [1]. CT has become the method of choice for evaluating the presence of ICH [2]. Patients with suspected ICH who have new onset of neurological deficits must undergo CT; however, some patients with signs/symptoms suggestive of ICH do not have new onset of neurological deficits that can be clearly identified, making it hard for the clinician to decide if brain CT scanning is needed. Usually clinicians will observe these patients initially. If the condition of the patient worsens then CT will be ordered. It would be desirable to reduce the time of medical observation and to reduce the number of CT scans carried out for patients with suspected ICH who do not have new onset of neurological deficits by using a screening test. One possible such screening test could be the D-dimer assay.

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D-dimer is a product of fibrin degradation. Quantitative measurement of circulating D-dimer levels has been shown to be a very useful diagnostic tool. Under certain circumstances, normal D-dimer level almost excludes the presence of thromboembolic disease, such as acute pulmonary embolism and deep vein thrombosis [3-5]. Circulating D-dimer level has also been shown to be elevated in patients with spontaneous intracranial hemorrhage (SICH), especially when a hematoma extends into the subarachnoid space [6]. Therefore, D-dimer assay offers a useful laboratory tool for assessing early and late clinical severity of subarachnoid hemorrhage (SAH) [7]. Elevated D-dimer levels also have been associated with poor clinical condition and outcome in patients with aneurysmal SAH and acute intracerebral hemorrhage [8-11]. Techniques for the quantitative detection of circulating D-dimer have improved so that the assay is now inexpensive and readily available [1]. D-dimer can be detected in serum using a variety of different assays including enzyme-linked immunosorbent assay (ELISA) (results in >8 hours), quantitative rapid ELISA (results in 30 minutes), semi-quantitative rapid ELISA (results in 10 minutes), qualitative rapid ELISA (results in 10 minutes), quantitative latex agglutination assay (results in 10 to 15 minutes), semi-quantitative latex agglutination assay (results in 5 minutes), and erythrocyte agglutination assay (SimpliRED) (results in 2 minutes) [1, 4]. For the quantitative assays, a level >500 ng/ml is usually considered abnormal [4].

If D-dimer can be used to exclude the possibility that patients with acute headache, acute vertigo, nausea, and vomiting but without new onset of neurological deficits have SICH it would help reduce the time required for medical observation and the number of CT examinations so that patients could get appropriate treatment as soon as possible in the ED. This study was conducted to assess whether D-dimer assay alone can be used for determining whether or not CT scanning is required for non-traumatic patients in the ED with symptoms and signs suggestive of SICH but without new onset of neurological deficits.

Materials and methods

Patients

Consecutive, non-traumatic patients admitted to the Chia-Yi Chang Gung Memorial Hospital (a stroke referral hospital) between December 2007 and April 2010 with symptoms and signs suggestive of SICH that would lead emergency physicians to consider whether to perform CT were prospectively recruited by emergency physicians to participate in this study. These patients comprise 0.6% of all patients at our hospital. The symptoms/signs included acute headache, acute vertigo, nausea, and vomiting. Acute headache was defined as headache within the previous 24 hours that had a severity that had never before been experienced. Vertigo/dizziness was defined as vertigo or dizziness within the previous 24 hours, absence of any neurological deficit, and poor response to medical treatment after 2 hours. Nausea or vomiting was defined as nausea or vomiting accompanied by headache or vertigo/dizziness within the previous 24 hours or decreased level of consciousness with vomiting and evidence of increased intracranial pressure such as the Cushing reflex. Patients were excluded if they had symptoms/signs of neurological deficits, including acute impaired consciousness, acute speech disturbance, acute sensory or motor impairment; the time between the onset of neurological symptoms and ED presentation was more than 24 hours; systolic blood pressure <100 mmHg; body temperature >38.5ºC; trauma within the past four weeks; thromboembolic diseases (such as deep venous thrombosis or pulmonary embolism) within the past four weeks; malignancy, acute nephrotic syndrome; signs of disseminated intravascular coagulopathy; pregnancy or termination of pregnancy within the past four weeks; or their age was less than 16 years.

The study was approved by the institutional review board of Chang Gung Memorial Hospital. Written informed consent was obtained from all participating patients or their family members, depending on whether the particular patients were conscious at the time.

Diagnostics studies

The patient's name, sex, age, phone number, related past medical history, onset of present illness, the time of arrival at the ED, current symptoms, vital signs (heart rate, respiratory rate, body temperature, blood pressure), initial level of consciousness, physical signs, and neurological findings were recorded. Emergency physicians performed the clinical assessments and trained research assistants collected the data using standardized data collection forms.

Non-contrast brain CT was performed within 30 minutes on patients with clinical suspicion of SICH. The CT slices were 4.8 mm thick. A positive brain CT scan was defined as finding ICH on CT, which was

confirmed by a radiologist. The clinical data collectors were blinded to the CT results. The scans were all re-evaluated by an experienced neuroradiologist who was blinded to the clinical data. Lumbar puncture was also performed if patients had severe headache that had never before been experienced and SAH was not demonstrated on brain CT but SAH was still suspected. Three patients underwent this procedure. Lumbar puncture was performed after brain CT confirmed that there was no brain edema to eliminate the danger of performing the procedure in the presence of intracranial hypertension. A positive lumbar puncture was defined as xanthochromia in the cerebrospinal fluid or red blood cells in the final sample of cerebrospinal fluid with positive results on angiography. One patient with a positive lumbar puncture underwent angiography. Only a few patients underwent lumbar puncture because this procedure is generally not acceptable to people who live in southern Taiwan.

Blood D-dimer level was measured on ED admission. VIDAS® D-Dimer Exclusion™ (BioMerieux, Durham, NC, USA) was used to quantify D-dimer (minimal detectable value: 50 ng/ml; a cutoff value of 500 ng/ml was empirically set by the clinical laboratory of the hospital). A level >500 ng/ml was defined as positive. VIDAS® D-Dimer Exclusion™ is a rapid, automated enzyme-linked immunosorbent assay (ELISA) test that can be performed quickly enough to use in the ED. To collect blood samples from a vein, a blood vacuum tube containing a buffer (3.2% sodium citrate) was used. The blood sample was transferred to the clinical laboratory within 30 minutes for D-dimer assay at room temperature. After the laboratory received the blood sample, the D-dimer assay was performed and the result was transmitted to the ED within one hour. Clinicians did not know the D-dimer level at the time they ordered CT. The results of D-dimer assay therefore were not used to decide whether patients required lumbar puncture.

Follow-up

All patients were followed up for one year including patients with negative results on CT who did not undergo lumbar puncture. The final diagnosis at 3 months follow-up was used to retrospectively determine whether brain CT was required when patients arrived at the ED and to make sure that there were no severe diseases such as subarachnoid hemorrhage that were misdiagnosed initially. Sometimes these severe disorders cannot be distinguished by CT and require confirmation by lumbar puncture assay.

Statistical analysis

All continuous variables were non-normally distributed and presented as median and inter-quartile range (IQR). Categorical variables were presented by count and percentage. Non-parametric Mann-Whitney test was performed to compare continuous data between the two groups and Fisher's exact test was performed for the associations between categorical variables. The Spearman correlation coefficient (ρ) was used for associations between D-dimer levels and hematoma volume and time to blood collection. Univariate and multivariate binary logistic regression models were used to assess the likelihood of CT scanning. The results of logistic regression models were presented as odds ratio (OR) and the corresponding 95% confidence interval (CI). The variables that reached statistical significance level in the corresponding univariate model were selected in the multivariate model by the forward conditional stepwise method. Area under the curve (AUC) analysis was performed to show the accuracy of the multivariate model. The statistical significance level was set at 0.05. All statistical results were performed using SPSS 15.0 statistics software (SPSS Inc, Chicago, IL, USA).

Results

The study included 90 patients. Seven (7.8%) patients had SAH, 13 (14.4%) had intracerebral hematoma, and one (1.1%) had intraventricular hemorrhage; no patient had subdural hematoma. There were also seven patients who had ischemic stroke and one who had hydrocephalus. According to the final diagnosis, it was unnecessary for 60 of the 90 patients to undergo CT when they were admitted to the ED (group I). In contrast, the other 30 patients should have undergone CT immediately when they were admitted to the ED (group II). To avoid unnecessary CT examinations we attempted to identify factors that affect whether CT is required for a particular patient.

Table 1 summarizes the patient demographic and clinical characteristics. The patients in group II were significantly older than those in group I (72.5 vs. 61.5 years; $p = 0.005$). With regard to symptoms,

a much higher proportion of patients in group II had dizziness or vertigo than in group I (73.3% vs. 43.3%, $p = 0.008$). With respect to vital signs, the two groups were significantly different in Glasgow Coma Scale (GCS) score. About 10% of patients in group I had GCS scores within the range of 3 to 14 compared to about 30% in group II ($p = 0.023$). Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher in group II than in group I (SBP 171.0 mmHg vs. 143.5 mmHg, $p < 0.001$; DBP 92.0 mmHg vs. 84.5 mmHg, $p = 0.008$). With regard to thromboplastic function, patients in group II had significantly lower prothrombin time (PT) than patients in group I ($p = 0.042$). The results of D-dimer assay showed that D-dimer level was significantly higher in group II than in group I (797.8 ng/ml vs. 382.8 ng/ml, $p = 0.009$); 70.0% of patients in group II had d-dimer >500 ng/ml compared with only 40.0% in group I ($p = 0.013$). There was no significant correlation between D-dimer level and hematoma volume (ñ = 0.082; $p = 0.0762$; n = 16), There was also no significant correlation between D-dimer level and time to blood collection (ñ = -0.135; $p = 0.206$; n = 89).

Table 1. Summary of patient demographic and clinical characteristics

		Diagnosis in the emergency department		*P* value
		Group I (n = 60)	**Group II (n = 30)**	
Demographics				
Age (years)		61.0 (45.5, 76.0)	72.5 (65.0, 81.0)	0.005*
Gender	Male	25 (41.7%)	13 (43.3%)	1.000
	Female	35 (58.3%)	17 (56.7%)	
History of old stroke		12 (20.0%)	12 (40.0%)	0.075
Symptoms				
Headache		30 (50.0%)	10 (33.3%)	0.178
Dizziness/vertigo		26 (43.3%)	22 (73.3%)	0.008*
Nausea/vomiting		18 (30.0%)	13 (43.3%)	0.244
Lumbar puncture (LP) result		2 (3.3%)	1 (3.3%)	1.000
Vital signs				
GCS	(3-8)	1 (1.8%)	5 (16.7%)	0.023*
	(9-12)	4 (7.0%)	2 (6.7%)	
	(13-14)	1 (1.8%)	2 (6.7%)	
	(15)	51 (89.5%)	21 (70.0%)	
Body temperature (!)		36.6 (36.1, 36.8)	36.5 (36.0, 37.3)	0.870
Pulse rate (beats/min)		79.5 (73.0, 94.0)	79.0 (70.0, 91.0)	0.629
Respiratory rate (breaths/min)		18.0 (17.0, 20.0)	18.0 (18.0, 20.0)	0.585
SBP (mmHg)		143.5 (127.5, 162.0)	171.0 (153.0, 210.0)	<0.001*
DBP (mmHg)		84.5 (73.0, 93.5)	92.0 (81.0, 113.0)	0.008*
Thromboplastic function				
PT (sec)		11.5 (11.1, 12.2)	11.1 (10.7, 11.9)	0.042*
APTT (sec)		26.4 (24.7, 28.8)	25.7 (24.4, 26.8)	0.241
D-dimer (μg/L)		382.8 (247.6, 1,188.0)	797.8 (448.8, 1,708.6)	0.009*
D-dimer >500 μg/L		24 (40.0%)	21 (70.0%)	0.013*

GCS = Glasgow Coma Scale, SBP = systolic blood pressure, DBP = diastolic blood pressure, PT = prothrombin time, APTT = activated partial thrombin time, Group I = patients who did not need to undergo CT after ED admission based on the final diagnosis, Group II = patients who should have undergone CT after ED admission based on the final diagnosis. Asterisks indicate statistical significance.

Table 2 summarizes the factors that affect whether CT is required. In the univariate analysis, seven variables reached significance level: D-dimer >500 ng/ml, age, history of stroke dizziness or vertigo, GCS score, SBP and DBP. In the multivariate analysis, three of these variables—dizziness/vertigo, SBP >120 mmHg, and D-dimer >500 ng/ml—had independent impacts on CT scanning. When taking into account the other two variables, patients who had the symptom of dizziness/vertigo were more likely to need CT scanning immediately than those without dizziness/vertigo (OR 3.65), and patients who had D-dimer level >500 ng/ml were more likely to need CT immediately than those who had D-dimer <500 ng/ml, (OR 3.80). The possibility of requiring CT scanning was slightly increased by each unit increase of SBP (OR 1.02).

Eight methods were used based on the three impact factors in the multivariate logistic regression model, and the corresponding sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each method are summarized in **Table 3**. Method 1 was based on the predictions in the multivariate logistic regression model in **Table 2**. The sensitivity was 100% and the specificity was 25%, which means that one-fourth of the patients could avoid CT scanning by the method. Method 7 was based on D-dimer >500 μg/L or the presence of dizziness or vertigo; the sensitivity was 96.7% and the specificity 28.8%, which means that 28.8% of the patients could avoid CT scanning by the method.

The D-dimer level by specific disease for those patients who required CT (group II) is shown in **Figure 1**. All patients with SAH had a D-dimer level >500 μg/L, and these patients had a significantly higher median D-dimer level than patients who had intracerebral hemorrhage or ischemic stroke (median: 1872.83 μg/L vs. 804.29 μg/L and 448.75 μg/L, $p = 0.003$ and $p = 0.001$, respectively).

Table 2. Summary of factors affecting the need for CT examinations

		Univariate		Multivariate	
		OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Demographics					
Age (years)		1.04 (1.01, 1.08)	0.005*		
Gender	Male	1.07 (0.44, 2.60)	0.880		
	Female	-			
History of old stoke		2.67 (1.01, 7.01)	0.047*		
Symptoms					
Headache		0.50 (0.20, 1.25)	0.136		
Dizziness/vertigo		3.60 (1.38, 9.36)	0.009*	3.65 (1.18, 11.27)	0.024*
Nausea/vomiting		1.78 (0.72, 4.43)	0.212		
Lumbar puncture (LP) result		1.00 (0.09, 11.49)	1.000		
Vital signs					
GCS	0 (15)	-			
	1 (13-14)	4.86 (0.42, 56.49)	0.207		
	2 (9-12)	1.21 (0.21, 7.14)	0.830		
	3 (3-8)	12.14 (1.34, 110.29)	0.027*		
Body temperature (!)		1.18 (0.67, 2.09)	0.562		
Pulse rate (beats/min)		1.00 (0.98, 1.02)	0.984		
Respiratory rate (breaths/min)		1.08 (0.88, 1.33)	0.470		
SBP (mmHg)		1.03 (1.01, 1.04)	<0.001*	1.02 (1.01, 1.03)	0.008*
DBP (mmHg)		1.04 (1.01, 1.06)	0.006*		
Thromboplastic function					
PT (sec)		0.76 (0.47, 1.22)	0.260		
APTT (sec)		0.96 (0.82, 1.12)	0.595		
D-dimer > 500 μg/L		3.50 (1.37, 8.93)	0.009*	3.80 (1.26, 11.45)	0.018*

GCS = Glasgow Coma Scale, SBP = systolic blood pressure, DBP = diastolic blood pressure, PT = prothrombin time, APTT = activated partial thrombin time. Asterisks indicate statistical significance. Area under the curve (AUC) obtained to 0.814 with the 95% CI of (0.722, 0.906).

Table 3. Sensitivity, specificity, NPV, and PPV for eight different methods

Methods	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1 Predictions from logistic regression model more than 0.0718	100.0	25.0	39.2	100.0
2 D-dimer >500 μg/L	70.0	59.3	46.7	79.5
3 SBP >120 mmHg	100.0	11.7	36.1	100.0
4 Dizziness/vertigo	73.3	56.7	45.8	81.0
5 D-dimer >500 μg/L or SBP>120 mmHg or dizziness/vertigo	100.0	1.7	34.1	100.0
6 D-dimer >500 μg/L or SBP>120 mm Hg	100.0	3.4	34.5	100.0
7 D-dimer >500 μg/L or dizziness/vertigo	96.7	28.8	40.8	94.4
8 SBP >120 mmHg or dizziness/vertigo	100.0	10.0	35.7	100.0

PPV = positive predictive value, NPV = negative predictive value, SBP = systolic blood pressure

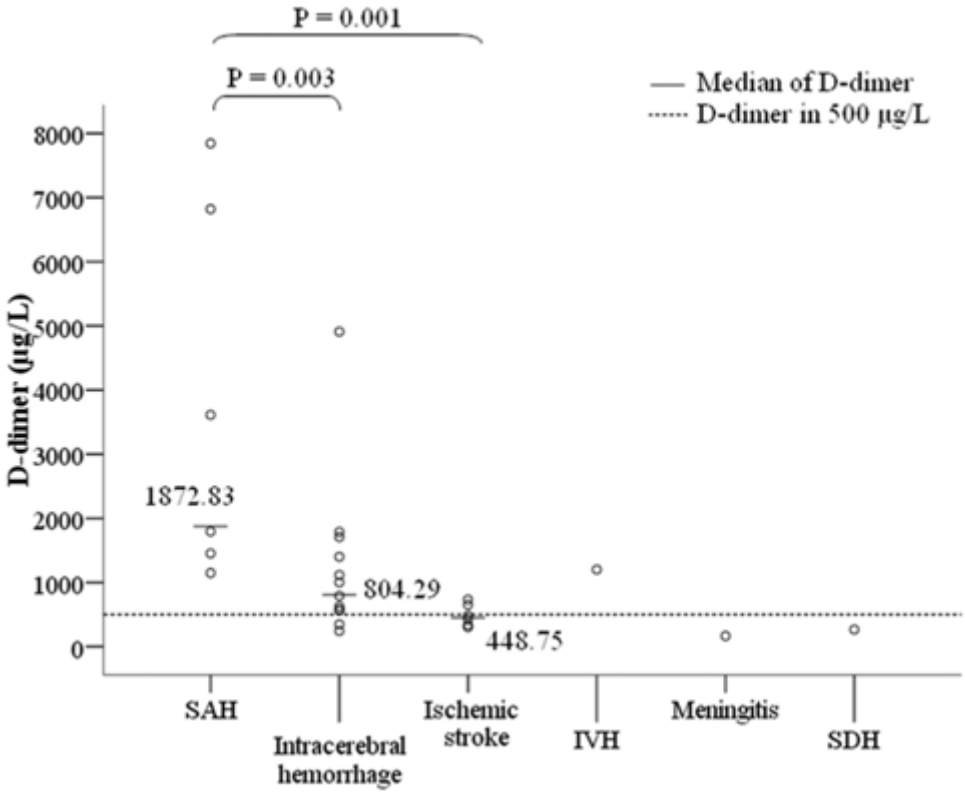

Figure 1. Summary of D-dimer levels in group II by disease. The 30 patients in group II included seven with subarachnoid hemorrhage (SAH), 13 with intracerebral hemorrhage, seven with ischemic stroke, one with interventricular hemorrhage (IVH), one with meningitis, and one with subdural hemorrhage (SDH). The D-dimer level in patients with SAH was significantly higher than those with intracerebral hemorrhage or ischemic stroke.

During one year of follow-up, five patients in group I and two patients in group II were lost to follow-up. There were no deaths among the patients in group I but four patients in group II died. One patient in group I had brain stem infarction during the one-year follow-up period.

Discussion

We studied 90 non-traumatic patients with signs and symptoms suggestive of SICH who did not have new onset of neurological deficits at ED admission to investigate whether using D-dimer assay alone to screen such patients could reduce the number of

CT scans. Based on the results of CT at three months follow-up and of lumbar puncture in three patients, it was determined that CT was not helpful for 60 patients at ED admission. A statistical analysis comparing the patients for whom CT was or was not helpful for making the diagnosis showed that three factors—D-dimer level, dizziness/vertigo, and systolic blood pressure >120 mmHg—were independently related to whether a CT examination was necessary after admission to the ED. D-dimer >500 μg/L alone had a sensitivity of only 70% (**Table 3**). Therefore, our results indicate that D-dimer assay alone is not adequate as a screening tool for determining which patients with suspected SICH and no new neurological deficits require a CT examination. Our hypothesis is therefore rejected. Additional analysis showed that among patients who required CT those who had SAH all had D-dimer levels >500 μg/L and their median D-dimer level was significantly higher than that of patients with intracerebral hemorrhage or ischemic stroke, suggesting that D-dimer level is more specifically related to SAH.

Previous studies have evaluated hemostasis and fibrinolysis activation after SAH [12]. An association between coagulopathy at admission and poor neurological outcome was confirmed [8-10]. One study concluded that the D-dimer assay was not adequately sensitive or predictive to be used as a screening tool for traumatic or spontaneous ICH [1]. This was a prospective study of 319 patients with suspected ICH who had a serum D-dimer assay obtained before undergoing CT. Twenty-five of the patients has a positive CT scan for ICH. The D-dimer assay had four false-negative results and the sensitivity was therefore 84.0%. Differences between this study and our study might explain why we obtained better results. The earlier study included patients with traumatic ICH and ours did not include any patients with a traumatic etiology. There were also differences in the D-dimer assay that was used. We used the VIDAS® D-Dimer Exclusion™, which is an automated ELISA test and the previous study used an automated latex enhanced immunoassay. Another difference between the studies is that we included two other factors that influence the requirement for CT scanning, SBP >120 mmHg and dizziness/vertigo, and we used a logistic regression model and multivariate analysis.

D-dimer has been reported to be potentially useful for screening of patients with other conditions. One such condition is suspected cerebral venous thrombosis. The presentation of cerebral venous thrombosis is often non-specific, with headache being the most common symptom [13]. A recent study in 18 patients has shown that D-dimer concentration has a high negative predictive value, since a D-dimer concentration <550 ng/ml allows exclusion of the diagnosis of cerebral venous thrombosis in patients with headache [14]. Sinus thrombosis is uncommon but is catastrophic in nature if the diagnosis is missed. D-dimer may be helpful for the evaluation of patients who present at the ED with acute headache.

Studies have also been carried out to assess the value of D-dimer assay for prognosis. In one study, it was found that increased level of plasma D-dimer is a predictor of poor outcome following acute intracerebral hemorrhage [9]. In another study [8], high level of plasma D-dimer was strongly associated with severe delayed ischemic deficit in patients who had spontaneous SAH. We found that elevated D-dimer level was closely related with the presence of SAH. All patients with SAH in our study had a D-dimer level >500 μg/L. This suggests that D-dimer assay might be particularly useful for identifying these patients. Four of our seven patients with SAH had severe headache. These patients comprised 10% of the 40 patients in our study with severe headache. This percentage is similar to that found by Perry et al who performed a prospective cohort study that included 1999 patients with severe headache [15]. They found that among 1,546 patients who complained of having the worst headaches in their life 130 (8.4%) had SAH.

Based on our findings we recommend that for patients who have acute headache, acute vertigo, nausea, and vomiting, but do not have new onset of neurological deficits the clinician can choose to observe these patients or immediately order a CT examination. Patients with dizziness/vertigo, SBP >120 mmHg, and D-dimer >500 ng/ml should immediately undergo a CT examination.

One limitation of our study was that the D-dimer assay is not a standardized test among various facilities. We evaluated just one of several types of ELISA D-dimer assays. Various D-dimer assays, however, have been found to have similar sensitivities and specificities for coagulopathy in evaluation for deep venous thrombosis [16]. Another limitation was that patients who were discharged from the ED with normal CT scans and false-positive D-dimer assays did not have sufficient follow-up with repeated CT scanning to be fully assessed for delayed injury.

Conclusions

Our findings indicate that initial screening with D-dimer assay alone of non-traumatic patients who present in the ED with symptoms and signs suggestive of SICH but without new onset of neurological deficits is not adequate for reducing the number of CT scans. This assay appears to be particularly specific for SAH.

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