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Clinical Value Of D-Dimer and Other Coagulation Markers in Differantial Diagnosis of Hemorrhagic and Ischemic Stroke

Hemorajik ve İskemik İnme Ayırıcı Tanısında D-Dimer ve Diğer Koagülasyon Belirteçlerinin Değerliliği

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ABSTRACT

PURPOSE: This study aims to determine the clinical value of some laboratory markers(D- dimer, Fibrinogen, etc levels) as alternatives to expensive and sometimes unavailable advanced radiographic techniques, in differentiation and early diagnosis of hemorrhagic and ischemic stroke which require distinct diagnosis, monitoring and treatment methods.

MATERIALS AND METHODS: The study includes 100 adult patients who applied to Emergency Department of Uludag University with clinical symptoms of stroke. At presentation on all of the patients and D-dimer, fibrinogen and other laboratory tests were studied. For differentiation of hemorrhagic and ischemic stroke, computerized tomography(CT) and magnetic resonance imaging(MRI) were taken. CT and MRI detections were assessed by radiology specialists blindly.

FINDINGS: Of 100 patients included in the study, 53% were women and 47% were men. In 28% of the patients, ischemic stroke, in 21%, hemorrhagic stroke and in 48%, transient ischemic attack (TIA) was detected, while remaining 3% were assessed as normal. Average age of patients with ischemic stroke was found higher than that of patients with hemorrhagic stroke. No significant difference was observed when patients were grouped by sexes. Coagulation markers, D-dimer and aPTT were significantly different between hemorrhagic stroke and TIA groups while no significant difference was observed between ischemic and hemorrhagic stroke groups.

RESULTS: Ischemic and hemorrhagic strokes cause homeostatic anomalies besides the brain damage accompanying. In our study, a difference between hemorrhagic stroke and TIA groups was observed, while no difference was found between ischemic and hemorrhagic stroke groups regarding coagulation markers.

Key words: Stroke, Transient ischemic attack, Coagulation markers, Differential diagnosis.

ÖZET

AMAÇ: Bu çalışma tanı, takip ve tedavisi farklı olan iskemik ve hemorajik strokların ayrımında ve erken tanısında pahalı ve her zaman elde bulunmayan ileri radyolojik görüntüleme teknikleri yerine laboratuarda bakılabilen bazı belirteçlerin (D-dimer, Fibrinojen vb) değerlerliliğini tespit etmek amacıyla yapılmıştır.

YÖNTEM-GEREÇLER: Uludağ Üniversitesi Acil Servisine strok kliniğiyle başvuran 18 yaş üstü 100 erişkin hasta çalışmaya dahil edilmiştir. Tüm hastalardan başvuru anında D-dimer, Fibrinojen ve diğer laboratuar tetkikleri istenmiştir. Çalışmaya alınan hastalarda hemorajik ve iskemik strok ayrımı için, kranial kompüterize Tomografi (CT) ve kranial Manyetik Rezonans Görüntüleme (MR) çekilmiştir. CT ve MR tetkikleri uzman radyologlar tarafından kör olarak değerlendirilmiştir.

BULGULAR: Çalışmaya alınan 100 hastanın %53'ü kadın ve %47'si erkekti. %28 olguda iskemik strok, %21 olguda hemorajik strok, %48 olguda geçici iskemik atak (GİA) saptanmış olup, kalan %3 olgu ise, normal olarak değerlendirildi. İskemik stroklu olguların yaş ortalaması anlamlı olarak kanamalı olgulardan daha yüksek saptandı. Cinsiyete göre bakıldığında ise, her iki grup arasında anlamlı fark saptanmadı. Koagülasyon belirteçlerine göre ise; hemorajik strok ve GİA grubu arasında D-dimer ve aPTT değerleri anlamlı farklılık gösterirken, iskemik ve hemorajik strok arasında istastistiksel olarak anlamlı farklılık saptanmadı.

SONUÇLAR: İskemik ve hemorajik stroklar beraberinde meydana gelen beyin hasarından hariç hemostatik anormalliklere de neden olmaktadırlar. Bizim çalışmamızda hemorajik strok ve GİA grubu arasında koagülasyon parametreleri açısından fark saptanırken, hemorajik ve iskemik stroklu olgular arasında ise fark saptanmamıştır.

Anahtar Kelimeler: İnme, Geçici iskemik atak, Serum belirteçleri, Ayırıcı tanı.

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INTRODUCTION

Acute stroke is one of the major causes of mortality and morbidity in the whole world. Though it is usually a disease of older population, 1/3 of the cases are younger than 65 years [1]. Especially after age of 55, incidence of stroke increases by double. Stroke is a real medical emergency and may revert without permanent damage by early diagnosis and treatment. Therefore emergency department physicians have an important role. Twenty per cent of patients with stroke die in the first year. Stroke imposes high costs due to the diagnosis, treatment and care of patients [2].

Strokes are classified into two groups: ischemic strokes resulting from blood vessel blockage that deprives neurons of oxygen and nutrients and hemorrhagic strokes caused by rupture of blood vessels due to trauma, intracranial pressure or mass effect. Ischemic stroke accounts 80 to 85 % of all cases. Ischemic strokes are further classified in 3 types as, embolic, thrombotic and hypoperfusion strokes. Most common is thrombotic stroke and usually develops progressively to reach to its maximum in minutes and hours and then intensifies. One fifth of stroke cases are embolic. Hypoperfusion strokes are less common. Hemorrhagic strokes divide in two major groups as intracranial and subarachnoid hemorrhages where intracranial hemorrhages account more of the cases [2, 3].

According to previous studies, impact of the disease lessens by early diagnosis and treatment of patients presented to emergency departments with stroke [4].

Presenting to emergency departments with acute stroke is very widespread. Diagnosis, monitoring and treatment of these patients is very time consuming and expensive. Currently, advanced diagnostic methods are employed in diagnosis, utilizing both laboratory and radiography.

Treatment approaches change with the stroke's being hemorrhagic or ischemic. In differential diagnosis, various radiological detection techniques such as computerized tomography (CT), angiography CT (CTA) and cranial magnetic resonance imaging (MRI) are used. Involvement of these imaging techniques depends on the presence of them, general state of the patient and indication by the clinician. Although many studies have been made on their superiority on each other, most preferred and accessible detection is CT in our country and in the world. However most of the ischemic strokes do not appear on CT earlier than 6 hours. Depending on the size of the infarct, this period may be longer. MRI can image ischemic strokes earlier than CT and is more efficient in detection of posterior circulation. On the other hand CT is superior in imaging hemorrhagic strokes [5-8].

Mentioned radiologic detections are time consuming, costly and not available at every medical facility. Therefore, transfer to a more advanced medical center may be necessary to accurately diagnose the disease and start the treatment as soon as possible.

There have been studies on employing some laboratory markers besides advanced radiologic methods in differential diagnosis of ischemic and hemorrhagic stroke which have completely different monitoring and treatment approaches [9-11], because strokes cause other hemostatic anomalies in addition to brain damage (12). One of those markers is a fibrin degradation product that increases with thromboembolic diseases, namely D-dimer, analysis of which is not expensive and can be measured by standard laboratory methods [13].

This study aims to determine the diagnostic value of some laboratory markers (D-dimer, Fibrinogen, PT, aPTT, INR, Thrombocyte levels) as alternatives to expensive and sometimes unavailable advanced radiographic techniques, in differentiation and early diagnosis of hemorrhagic and ischemic stroke which require distinct diagnosis, monitoring and treatment methods.

MATERIALS AND METHODS

Hundred adult patients (older than 18) who presented to Emergency Department of Uludag University with clinical symptoms of stroke were included in the study. At presentation electrocardiogram (ECG) were performed for all the patients and D-dimer, fibrinogen, complete blood count, PT, aPTT, INR and other laboratory tests were studied. For differentiation of hemorrhagic and ischemic stroke, CT and cranial MRI were taken. CT and MRI detections were assessed by radiology specialists blindly. All the clinical, radiologic and laboratorial data was recorded on work forms previously prepared. The study was supported by Uludag University Rectorship Scientific Research Projects Committee (01 Dec 2006 / 2006-4) and was approved by the ethical committee (decree dated 29 Jun 2004 and numbered 2004-15/10).

Pregnant patients and patients with infection, malignity, inflammatory disease, peripheral vessel disease, pulmonary thromboembolism, recent trauma or operation history accompanying clinical symptoms of stroke were excluded.

A form prepared prior to the study was filled for patients admitted to emergency department with suspicion of stroke. Patient information such as name-surname, age, sex, protocol number, arrival date-time, address and phone number were filled on this form in addition to accompanying diseases and vital parameters such as the complaint at presentation, starting time of the complaints, symptoms, blood pressure and breath rate per minute. On each patient 12 derivation ECG was performed and rhythm analysis was conducted. Glasgow Coma Scale scores (GCS) were computed. Blood samples were taken from patients for complete blood count, D-dimer, fibrinogen (Sysmex® CA-1500 System), PT, aPTT and INR measurements. On each patient CT was performed and cranial diffusion MRI scans were made for patients with normal tomography. Results of laboratory tests and radiological imaging were also recorded in the form. Finally, diagnoses of patients and the outcomes (hospitalization, discharge, transfer or death) were noted in the form. Statistical analyses on study data were performed using SPSS for Windows version 10.0. Results were expressed as average ± standard deviation. Statistical significance of differences was evaluated using Pearson's chi-square, Kruskal-Wallis and Mann-Whitney U tests. Differences with p value less than 0.05 were assumed statistically significant.

RESULTS

Of 100 patients included in the study, 53 % were women and 47 % were men. In 28 % of the patients, ischemic stroke; in 21 %, hemorrhagic stroke; and in 48%, transient ischemic attack (TIA) was detected, while remaining 3 % were assessed as normal. Average age of patients with ischemic stroke was 67.2 ± 13.1 while in patients with hemorrhagic strokes it was 57.4 ± 15.4 (Table-1). Average age of patients with ischemic stroke was found to be significantly higher than that of patients with hemorrhagic stroke (p=0.008). Each one unit increase in age was increasing probability of blockage by 0.5 to 1 %. No significant difference was observed between ischemic and hemorrhagic stroke incidences according to Pearson chi-square test when patients were grouped by sexes (p>0.05).

Distribution of patients according to GCS was as follows: 74% patients with GCS≥13, 15% with GCS=8-12 and 11% with GCS≤ 7 (Table-2). Six of the 15 patients with GCS=8-12 had hemorrhagic stroke and the remaining 9 had ischemic stroke. Eight of the 11 patients with GCS ≤ 7 had hemorrhagic stroke while only 3 had ischemic stroke. GCS scores of patients with hemorrhagic stroke were significantly lower. Fibrinogen levels of 65 of 100 patients included in the study were found to be high (>3.5 g/L) and of these patients 24.6 % had TIA, 43.1% had ischemic stroke, and 32.3% had hemorrhagic stroke.

Number of patients with high D-dimer levels (>375 µg/L) was 32 and 50% of these were hemorrhagic stroke, 43.8% were ischemic stroke and 6.2% were TIA. There were 10 patients with high levels of PT (>15 s), aPTT (>31 s) and INR (>1.2). 10% of these had hemorrhagic stroke, 30% had TIA and 60% had ischemic stroke (table-3). Number of patients with low thrombocyte counts (<150 K/µL) was 3 and all of these had ischemic stroke.

Coagulation markers, D-dimer and aPTT were significantly different between hemorrhagic stroke and TIA groups while no significant difference was observed between ischemic and hemorrhagic stroke groups regarding coagulation markers. Univariate and multivariate regression analyses were performed to determine whether a predictive risk factor could be identified from blood values, age and sex. No statistical significance was observed except for age itself (OR=1.051 [1.013-1.089] 95% confidence interval).

On ECG evaluations, atrial fibrillation (AF) was detected in 15 patients and 85 patients had normal sinus rhythm in ECG. Of 15 patients with AF, 14 had ischemic stroke and 1 had TIA. As for the outcomes, 46% of patients were hospitalized, 40% were transferred to another healthcare organization, 13% were discharged and 1% died in the emergency department.

Table-1: Distribution of stroke types by age groups

Stroke types	%	Mean Age ± SD (years)
Ischemic stroke	28	67.2 ± 13.1
Hemorrhagic stroke	21	57.4 ± 15.4

Table-2: Distribution of patients by Glasgow Coma Scale score (GCS

GCS	%
GCS ≥13	74
GCS=8-12	15
GCS ≤7	11

Table-3: Values of coagulation markers in Hemorrhagic Stroke, Ischemic Stroke and Transient Ischemic Attack (TIA) groups

Coagulation markers	Hemorrhagic Stroke		Ischemic Stroke		TIA		Total
	n	%	n	%	n	%	
D-dimer (>375 µg/L)	16	% 50	14	%43.8	2	%6.2	32
Fibrinogen (>3.5 g/L)	21	32.3	28	%43.1	16	%24.6	65
PT / aPTT / INR (>15s / >31s / >1.2)	1	%10	6	%60	3	%30	10

DISCUSSION

Li F and colleagues have found in their study with 35 patients that the concentrations of D-dimer, tissue plasminogen activator (t-PA), plasminogen activator inhibitor (PAI-1) and plasminogen activity (PLG) in cerebrospinal fluid and plasma in patients with acute cerebral infarction were higher than those of normal subjects [14]. Ageno W and colleagues have assessed the clinical utility of D-dimer in the early diagnosis of stroke subtypes and reported that at day 1, D-dimer was higher in cardioembolic patients than in lacunar and control group patients [15]. Similarly, Koch et al. [16], in a study covering 59 patients with ischemic stroke, have evaluated coagulation profiles within the first 24 hours after the onset of stroke symptoms and before anticoagulant treatment had been started and found that patients with cardioembolic stroke had significantly higher D-dimer concentrations than controls and patients with transient ischemic attacks. Finally Montaner et al. [17], in their study covering 707 patients with acute stroke, have suggested that the plasma markers like Brain Natriuretic Peptide (BNP) and D-dimer could be useful in differential diagnosis of cardioembolic stroke in the acute phase. In our study on the other hand, patients were grouped as having ischemic stroke, hemorrhagic stroke, TIA and others and no statistically significant difference could be found between these groups regarding coagulation markers.

Lip GY and colleagues in their study of 86 patients presented with acute stroke in less then 12 hours, have investigated anomalies of hemorheology (plasma viscosity, fibrinogen), endothelial dysfunction (von Willebrand factor), platelet activation (soluble P-selectin) and thrombogenesis (plasminogen activator inhibitor and fibrin D-dimer). They have found that the von Willebrand factor, plasminogen activator inhibitor soluble P-selectin and fibrin D-dimer

levels were higher in the acute stroke patients [18]. However, in that study they could not observe any significant difference in measured indices of hemorheology, endothelial dysfunction and thrombogenesis between the three stroke types (ischemic, hemorrhagic or TIA). In our study there was no significant difference between ischemic, hemorrhagic or TIA groups regarding D-dimer values while the difference between TIA and hemorrhagic group was found significant.

Antovic J and colleagues have investigated some blood coagulation and fibrinolysis parameters (PT, aPTT, fibrinogen, active FVII, antithrombin, plasminogen inhibitor (PI) and fibrin D-dimer) in 30 patients with ischemic stroke and 30 with hemorrhagic stroke. They have shown that fibrinogen and D-dimer levels increased significantly in both types of stroke [12]. Anzej S et al. in a study with young stroke patients, have reported similarly that fibrinogen, D-dimer, soluble P-selectin and CRP levels were higher than the control group levels (19). Smith et al. [20], in a study with middle aged male patients, have reported that the rise in the levels of D-dimer and fibrinogen was related with risk in both ischemic stroke and coronary heart diseases. In our study, fibrinogen level was high in %65 and D-dimer was high in 32% of 100 patients.

De Moerloose P and colleagues have suggested by their article that D-dimer level increases after ischemic stroke and TIA, however they stated that this should be confirmed by new interesting findings like thriving researches defining the best treatment regime involving D-dimer concentration together with clinical findings and imaging methods [13]. In our study, while statistically significant difference was found in D-dimer and aPTT values between the hemorrhagic stroke and TIA group, no statistically significant difference was detected in coagulation markers between hemorrhagic and ischemic stroke groups. Our findings partially support this article.

In a retrospective study [21] of patients with acute cerebral infarct (CI), Dougu et al. have divided patients into 2 groups according to their being with or without atrial fibrillation (AF) prior to or at admission and examined CI rates and D-dimer levels. They found CI rate to be 82% in AF group and only 2% in non AF group. They observed significantly higher D-dimer levels in non AF patients with CI. In our study, AF was detected in ECG of 15 patients and 14 of these had ischemic stroke. Rate of ischemic stroke in AF patients was 93.3% while it was 16.5% in non AF patients. There were 14 patients without AF among 28 patients with ischemic stroke and D-dimer levels were high in all of them. Our findings show similarity to the study mentioned above.

Rallidis LS and colleagues [22] have monitored 231 middle aged patients with ischemic stroke and found that CRP, fibrinogen and D-dimer levels were significantly higher in 15 patients who died during hospitalization than in the survived. In our study, only 1 of 100 patients died in the emergency department and the D-dimer and fibrinogen levels of that patient were high.

In their study [23], Delgado P et al. have measured initial and follow-up (24 hours, 48 hours, 7th day, and 3rd month) D-dimer levels in 21 patients with acute intracerebral hemorrhage. They have observed that increased plasma D-dimer level was associated with early neurologic degeneration and poor outcome. Similarly, in their study [24], Juvela S et al. have demonstrated that elevated D-dimer levels might be useful in detecting poor prognosis in patients with aneurysmal subarachnoid hemorrhage. Contrary to the studies mentioned, Squizzato et al., [25] suggested that D-dimer marker had low specificity and sensitivity in acute stroke patients and therefore would not be useful in determining long term prognosis. Considered a missing aspect, the relation between D-dimer levels and long term prognosis was not examined in our study.

Ebihara and colleagues [26], in their study with 143 patients with intracranial hemorrhage, have measured blood levels of coagulative and fibrinolytic factors and found that patients with subarachnoid hemorrhage had higher levels than the patients with hypertensive intracerebral hemorrhage. Thus they deduced that coagulative/fibrinolytic cascade might have been activated via different mechanisms in different types of stroke. In our study D-dimer and aPTT levels showed significant difference between hemorrhagic stroke and TIA group regarding coagulation markers. However a significant difference between ischemic and hemorrhagic stroke was not detected.

Woodward et al. [27], in their study covering 591 stroke patients (83 hemorrhagic, 472 ischemic), has shown that fibrinogen level was significantly higher in patients with ischemic stroke. In our study, fibrinogen levels of 65 of 100 patients were high (>3.5 g/L) and of these patients 24.6% had TIA, 43.1% had ischemic stroke, and 32.3% had hemorrhagic stroke. However a significant difference of fibrinogen levels was not detected between ischemic and hemorrhagic stroke groups.

Acute stroke is a disease with high mortality and morbidity and its early diagnosis and treatment is important. Ischemic and hemorrhagic strokes cause hemostatic anomalies besides accompanying brain damage. From this point of view, some laboratory testable coagulation markers such as D-dimer and fibrinogen might help early diagnosis. In our study, a difference between hemorrhagic stroke and TIA groups was observed, while no difference was found between ischemic and hemorrhagic stroke groups regarding coagulation markers. Studies employing wider data series are necessary to assess the clinical value of these markers in differential diagnosis of ischemic and hemorrhagic strokes.

REFERENCES

1. M. Bulut, Ş.A.Aydın. Akut İnme. In: S. Satar, Ö. Karcıoğlu, editors. Kardiyak Aciller. 1st ed. İstanbul: Nobel Kitabevi; 2008. p.459.
2. Scott AP, Barsan WG. Stroke, Transient ischemic attack, and other central focal conditions. In: Tintinalli JE, Kelen GD, Stapczynski JS, eds. Emergency Medicine: A Comprehensive Study Guide. 5th ed. North Carolina: McGraw-Hill; 1999. pp. 1430-1439.
3. Warlow C, Dennis MS, van Gijn J, et al. Stroke. A practical guide to management. Oxford: Blackwell; 1996.
4. Emre U, Durukan A, Tatlısumak T. İskemik İnmede Acil Tanı ve Tedavi Yaklaşımları. Turkiye Klinikleri J Surg Med Sci. 2007;3:6-12.
5. Mullins ME, Schaefer PW, Sorensen AG, Halpern EF, Ay H, He J, et al. CT and conventional and diffusion-weighted MR imaging in acute stroke: study in 691 patients at presentation to the emergency department. Radiology. 2002;224:353-60.
6. Wintermark M, Bogousslavsky J. Imaging of acute ischemic brain injury: the return of computed tomography. Curr Opin Neurol. 2003;16:59-63.
7. Grunwald I, Reith W. Non-traumatic neurological emergencies: imaging of cerebral ischemia. Eur Radiol. 2002;12:1632-47.
8. Campbell BG, Zimmerman RD. Emergency magnetic resonance of the brain. Top Magn Reson Imaging. 1998;9:208-27.
9. Landi G, D'Angelo A, Boccardi E, Candelise L, Mannucci PM, Nobile Orazio E, et al. Hypercoagulobility in acute stroke:prognostic significance. Neurology. 1987;37:1667-71.
10. Takano K, Yamaguchi T, Kato H, Omae T. Activation of coagulation in acute cardioembolic stroke. Stroke. 1991;22:12-6.
11. Yamazaki M, Uchiyama S, Maruyama S. Alterations of haemostatic markers in varios subtypes and phases of stroke. Blood Coagulations Fibrinolysis. 1993;4:707-12.
12. Antovic J, Bakic M, Zivkovic M, Ilic A, Blomback M. Blood coagulation and fibrinolysis in subarachnoid haemorhage compared to other types of stroke?. Scan J Clin Lab Invest. 2002;62:195-9.
13. de Moerloose P, Boehlen F. Should neurogists measure D-Dimer concentrations?. Lancet Neurol. 2003;2:77.
14. Li F, Zhang G, Zhao W. Coagulation and fibrinolytic activity in patients with acute cerebral infarction. Chin Med J (Engl). 2003;116:475-7.
15. Ageno W, Finazzi S, Steidl L, Biotti MG, Mera V, Melzi D'Eril G, et al. Plasma measurement of D-Dimer levels for the early diagnosis of ischemic stroke subtypes. Arch Intern Med. 2002;162:2589-93.
16. Koch HJ, Horn M, Bogdahn U, Ickenstein GW. The relationship between plasma D-dimer concentrations and acut ischemic stroke subtypes. J Stroke Cerebrovasc Dis. 2005;14: 75-9.
17. Montaner J, Perea-Ganzia M, Delgado P, Ribo M, Chacon P, Rosell A, et al. Etiologic Diagnosis of Ischemic Stroke Subtypes With Plasma Biomarkers. Stroke. 2008;39:1-8.
18. Lip GY, Blann AD, Farooqi IS, Zarifis J, Sagar G, Beevers DG. Abnormal haemorheology, endothelial function and trombogenesis in relation to hypertension in acute (ictus<12h) stroke patients: the West Birmingham Stroke Project. Blood Coagul Fibrinolysis. 2001;12:307-15.
19. Anzej S, Bozic M, Antovic A, Peternel P, Gaspersic N, Rot U, et al. Evidence of hypercoagulability and inflammation in young patients long after acute cerebral ischaemia. Trombosis Research. 2007;120:39-46.
20. Smith A, Patterson C, Yarnell J, Rumley A, Ben-Shlomo Y, Lowe G. Which Hemostatic Markers Add to the Predictive Value of Conventional risk Factors for Coronary Heart Disease and Ischemic Stroke?. Circulation. 2005;112:3080-7.
21. Dougu N, Takashima S, Sasahara E, Taguchi Y, Toyoda S, Hirai T, et al. Differential diagnosis of cerebral infarction using an algorithm combining atrial fibrillation and D-dimer level. Eur J Neurol. 2008;15:295-300.
22. Rallidis LS, Vikelis M, Panagiotakos DB, Liakos GK, Krania E, Kremastinos DT. Usefulness of inflammatory and haemostatic markers to predict short-time risk for death in middle-aged ischaemic stroke patients. Acta Neurol Scand. 2008;117:415-20.
23. Delgado P, Alvarez-Sabin J, Abilleira S, Santamarina E, Purroy F, Arenillas JF, et al. Plasma d-dimer predicts poor outcome after acute intracerebral hemorrhage. Neurology. 2006;67:94-8.
24. Juvela S, Siironen J. D-dimer as an independent predictor for poor outcome after aneurysmal subarachnoid hemorrhage. Nat Clin Pract Neurol. 2006;2:592-3.
25. Squizzato A, Ageno W, Finazzi S, Mera V, Roumaldi E, Bossi A, et al. D-dimer is not a long-term prognostic marker following acute cerebral ischemia. Blood Coagulation and Fibrinolysis. 2006;17:303-6.
26. Ebihara T, Kinoshita K, Utagawa A, Sakurai A, Furukawa M, Kitahata Y, et al. Changes in coagulative and fibrinolytic activities in patients with intracranial hemorrhage. Acta Neurochir Suppl. 2006;96:69-73.
27. Woodward M, Lowe GD, Campbell DJ, Colman S, Rumley A, Chalmers J, et al. Associations of inflamatory and hemostatic variables with the risk of recurrent stroke. Stroke. 2005;36:2143-7.