

High-sensitivity C-reactive protein, lipoprotein-related phospholipase A₂, and acute ischemic stroke

Hasan Kara¹
Murat Akinci¹
Selim Degirmenci¹
Aysegul Bayir¹
Ahmet Ak¹
Alaaddin Nayman²
Ali Unlu³
Fikret Akyurek³
Mesut Sivri²

¹Department of Emergency Medicine, ²Department of Radiology, ³Department of Biochemistry, Faculty of Medicine, Selçuk University, Konya, Turkey

Background: Serum biomarkers may be useful for early diagnosis of acute ischemic stroke, exclusion of other diseases that may mimic stroke, and prediction of infarct volume. We evaluated serum high-sensitivity C-reactive protein (hs-CRP) and lipoprotein-related phospholipase A₂ (Lp-PLA₂) in patients who had acute ischemic stroke.

Methods: In 200 patients who presented to an emergency service (acute ischemic stroke, 102 patients; control with no stroke, 98 patients), stroke patients were evaluated with the Canadian neurological scale and diffusion-weighted magnetic resonance imaging, and all patients were evaluated with the Glasgow coma scale and their serum hs-CRP level and Lp-PLA₂ activity were assessed. The volume of stroke lesions was calculated from magnetic resonance images.

Results: Patients who had stroke had higher mean serum hs-CRP level (stroke, 7±6 mg/dL; control, mean ± standard deviation 1±1 mg/dL; $P \leq 0.001$) and Lp-PLA₂ activity (stroke, mean ± standard deviation 113±86 nmol/min/mL; control, mean ± standard deviation 103±50 nmol/min/mL; $P \leq 0.001$) than control patients who did not have stroke. The mean hs-CRP level and Lp-PLA₂ activity were higher in patients who had greater stroke severity (lower Canadian neurological scale score) and were higher in patients who had larger volume strokes.

Conclusion: Higher hs-CRP level and Lp-PLA₂ activity are significantly associated with more severe neurologic impairment and larger infarct size in patients who have acute ischemic stroke. These biomarkers may be useful for rapid diagnosis and prediction of ischemic tissue volume in the early stage of ischemic stroke. These findings may be important for health care facilities that have limited access to emergency computed tomography scanning for the diagnosis of stroke.

Keywords: cerebrovascular accident, atherosclerosis, inflammation, biomarker

Introduction

Acute ischemic stroke is caused by sudden interruption of cerebral blood flow. The causes of acute ischemic stroke in most patients who have severe symptoms include embolic or thrombotic occlusion (70% to 80% of patients).¹ Despite developments in treatment, acute ischemic stroke still is a leading cause of morbidity, mortality, and economic burden on society. Therefore, it is important to prevent acute ischemic stroke by determining and modifying risk factors. It is also important to minimize the duration from onset of symptoms to treatment to ensure effective reperfusion in patients who have acute ischemic stroke.

A major obstacle for patients suspected of having acute ischemic stroke is that diagnostic evaluation may not be provided quickly.^{2,3} Diagnosis and treatment of small

Correspondence: Hasan Kara
Department of Emergency Medicine,
Faculty of Medicine, Selçuk University,
Konya, Turkey 42250
Tel +90 505 211 2473
Fax +90 332 224 4858
Email hasankara42@gmail.com

strokes may be delayed because symptoms may be absent. Computed tomography (CT) has low sensitivity and specificity in the early stage of acute ischemic stroke. Although CT or magnetic resonance imaging (MRI) of the brain can be performed within 30 minutes, enabling diagnosis in the early stage of acute ischemic stroke, these imaging methods require an experienced team and technical equipment that are not available in many hospitals in our country.⁴

Thrombolytic treatment with tissue plasminogen activator within 3 hours after early diagnosis of acute ischemic stroke may decrease patient mortality and improve quality of life. Thrombolytic treatment is more effective in younger patients who have low National Institutes of Health stroke scale score and low infarct volume in diffusion-weighted imaging.⁵ Early diagnosis and calculation of infarct volume are important in assessing suitability of thrombolytic therapy, and only 2% to 6% of patients diagnosed with acute ischemic stroke may be treated with tissue plasminogen activator.⁶

Acute ischemic stroke is diagnosed with physical examination, CT scan, and MRI scan. Missed diagnosis and delayed treatment may occur because the specificity and sensitivity of CT scanning are low in the early stage of acute ischemic stroke, and CT and MRI scans are not available in many health care facilities. Therefore, diagnostic serum biomarkers may be useful for early diagnosis of acute ischemic stroke, exclusion of other diseases that may mimic stroke, and prediction of infarct volume.

Inflammation may cause atherosclerosis and plaque rupture that may cause myocardial infarction and acute ischemic stroke.⁷ High-sensitivity C-reactive protein (hs-CRP) and other serum inflammatory markers may be helpful in predicting carotid atherosclerosis and acute ischemic stroke. Lipoprotein-related phospholipase A₂ (Lp-PLA₂) is a proinflammatory enzyme that may hydrolyze oxidized phospholipids and cause the release of lysophosphatidylcholine.⁸ High hs-CRP level and Lp-PLA₂ activity may be complementary to established risk factors for the development of stroke.^{9,10}

The purpose of the present study was to evaluate serum hs-CRP level and Lp-PLA₂ activity in patients who had acute ischemic stroke and determine whether these factors may predict ischemic tissue volume.

Materials and methods

Study design

Patients who presented to Selçuk University School of Medicine Hospital Emergency Service from June 2012 to August 2013 were considered for inclusion in this prospective study

when they presented within 24 hours after onset of symptoms, were aged >18 years, and had findings in the initial history and physical examination that were consistent with acute ischemic stroke. The 102 patients who were included in the study group were diagnosed with acute ischemic stroke with diffusion-weighted MRI performed within 24 hours after presentation. The 98 patients who were included in the control group had presented to the emergency service with various complaints; were evaluated with physical examination, laboratory tests, and imaging studies; and were diagnosed with conditions other than acute ischemic stroke. Patients were excluded for cerebral hemorrhage, subdural hematoma, space-occupying lesion, cerebrovascular damage caused by trauma (detected on CT images performed in the emergency service), symptoms of infection, immunologic disease, malignancy, or pregnancy. All stroke and control patients gave informed consent before enrollment in the study. The study was approved by the Selçuk University School of Medicine Research Ethics Committee.

Evaluation

Patients who had acute ischemic stroke were evaluated with physical examination, neurologic examination, Glasgow coma scale, and Canadian neurological scale. The Glasgow coma scale was determined for patients in the control group, but the more detailed Canadian neurological scale was not determined for control patients. Severity of impaired level of consciousness was rated with the Glasgow coma scale score as mild (15), moderate (8 to 14), or severe (3 to 7). Severity of impaired neurologic status was rated by Canadian neurological scale score as mild (8.5 to 10), moderate (2.5 to 8), or severe (0 to 2). In addition to routine laboratory tests such as biochemistry tests and complete blood count, the stroke and control patients were tested for hs-CRP level, Lp-PLA₂ activity and underwent a 12-lead electrocardiogram.

Biochemistry

Blood samples were collected in plain plastic tubes during the emergency service admission. After standing for 30 minutes, the blood samples were centrifuged for 5 minutes at 3,000 rpm. The sera were separated and allocated to tubes (Eppendorf, Hamburg, Germany) and stored at -80°C until assay. The Lp-PLA₂ activity was determined with a commercial kit (DiaDexus, South San Francisco, CA, USA) and analyzer (Architect C8000; Abbott Laboratories, Abbott Park, IL, USA). Calibration and control procedures were performed, samples were dissolved, and enzyme activity (nmol/min/mL) was determined from absorbance at

412 and 524 nm. Serum Lp-PLA₂ activity was defined as low (<100 nmol/min/mL), medium (100 to 150 nmol/min/mL), or high (>150 nmol/min/mL).

The hs-CRP level was determined with a commercial kit (Abbott Laboratories) and analyzer (Architect C8000; Abbott Laboratories). After the samples were dissolved, a commercial test was performed (Denka Seiken, Tokyo, Japan) and validated by a commercial method (Dade Behring; Siemens Healthcare, Erlangen, Germany) and analyzed with a spectrophotometric method. The hs-CRP level was reported in mg/dL (reference range <0.5 mg/dL). Plasma hs-CRP level was defined as low (<3 mg/dL), medium (3 to 15 mg/dL) or high (>15 mg/dL). The assays were performed at the Selçuk University School of Medicine Biochemistry Laboratory.

Imaging

MRI scans were performed with a 1.5-T scanner (Aera; Siemens Healthcare). Diffusion-weighted imaging was performed with single-shot, echo-planar imaging (TE, 89 ms; TR, 6,300 ms; matrix, 128×128; b values, 0 and 1,000 seconds/mm²; slice thickness, 5 mm; gap, 1 mm; 20 slices). All MRI data were analyzed by an experienced radiologist who was blinded to clinical and laboratory information about the patients and location and number of

hyperintensities on diffusion-weighted imaging. The lesion volumes were calculated off-line after the images were transferred to an image postprocessing software package (*syngo*, via, Siemens Healthcare). The areas of diffusion hyperintensity were drawn manually by two observers, and the volume was determined by multiplying the areas of diffusion hyperintensity by the interslice gap. Infarcts were classified as nonlacunar or lacunar.

Statistical analysis

Data analysis was performed with statistical software (SPSS Statistics for Windows, version 20.0; IBM Corporation, Armonk, NY, USA). Data were evaluated with descriptive statistics, variance components analysis, and χ^2 test. Average results were reported as mean \pm standard deviation. Differences between the groups were analyzed with one-way analysis of variance. In addition, differences between stroke and control patients were assessed with cross tabulation and χ^2 test. Statistical significance was defined by $P \leq 0.05$.

Results

The patients who had or did not have stroke had similar sex, mean age, Glasgow coma scale score, and systolic blood pressure (Table 1). Patients who had stroke had higher mean

Table 1 Demographic and clinical characteristics of patients who had or did not have stroke

Characteristic	Stroke	Control	P-value
Number of patients	102	98	
Sex, male	58 (57)	45 (46)	NS
Age (years)	68 \pm 14	64 \pm 15	NS
Glasgow coma scale	14 \pm 2	15 \pm 2	NS
Canadian neurological scale	8 \pm 3	Not determined	
Blood pressure (mmHg)			
Systolic	138 \pm 25	130 \pm 31	NS
Diastolic	82 \pm 10	76 \pm 14	0.02
Symptoms			
Walking impairment	75 (74)	24 (25)	0.001
Speech impairment	54 (59)	32 (33)	0.003
Impairment in consciousness	24 (24)	15 (15)	NS
History			
Hypertension	41 (40)	34 (35)	NS
Diabetes mellitus	24 (24)	10 (10)	0.01
Coronary artery disease	27 (27)	19 (19)	NS
Recurrent stroke	20 (20)	13 (13)	NS
Electrocardiogram			
ST segment changes	39 (38)	30 (31)	NS
Arrhythmia	37 (36)	20 (20)	0.01
Normal sinus rhythm	27 (27)	47 (48)	0.001
Laboratory tests			
hs-CRP (mg/dL)	7 \pm 6	1 \pm 1	0.001
Lp-PLA ₂ (nmol/min/mL)	113 \pm 86	103 \pm 50	0.001

Notes: Data reported as number (%) or mean \pm standard deviation. Statistical significance was defined as $P \leq 0.05$.

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; Lp-PLA₂, lipoprotein-related phospholipase A₂; NS, not significant ($P > 0.05$).

Table 2 Relationship between neurologic status rated by the Canadian neurological scale and outcome parameters in patients who had acute ischemic stroke

Parameter	Total	Mild	Moderate	Severe	P-value			
		8.5 to 10	2.5 to 8	0 to 2				
Canadian neurological scale	Number of patients	Number of patients	Number of patients	Number of patients				
Glasgow coma scale	102	69	14.9±0.3	20	14±2	13	11±4	0.001
Nonlacunar infarct volume (mL)	48	23	20±23	17	51±69	8	69±62	0.05
Lacunar infarct volume (mL)	54	46	3±3	3	2±2	5	8±8	0.009
hs-CRP (mg/dL)	102	69	5±6	20	8±6	13	12±7	0.001
Lp-PLA ₂ (nmol/min/mL)	102	69	96±88	20	143±78	13	163±60	0.008

Notes: Data reported as number or mean ± standard deviation. Statistical significance was defined as $P \leq 0.05$.

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; Lp-PLA₂, lipoprotein-related phospholipase A₂.

diastolic blood pressure, higher frequency of walking and speech impairment, higher frequency of diabetes mellitus and arrhythmias, and higher mean hs-CRP level and Lp-PLA₂ activity than control patients (Table 1).

Increased severity of neurologic status rated by the Canadian neurological scale was associated with lower mean Glasgow coma scale, larger volume of nonlacunar or lacunar stroke, and higher hs-CRP level and Lp-PLA₂ activity (Table 2). Increased impairment of consciousness rated by Glasgow coma scale was associated with lower mean Canadian neurological scale score and higher hs-CRP level but not infarct size or Lp-PLA₂ level (Table 3). Higher hs-CRP level and Lp-PLA₂ activity were significantly associated with larger volume of nonlacunar and lacunar infarcts, except medium Lp-PLA₂ levels were associated with highest mean volume of lacunar infarcts (Tables 4 and 5).

Discussion

The present results showed that higher hs-CRP level and Lp-PLA₂ activity were significantly associated with more severe neurologic impairment and larger infarct size in patients who had acute ischemic stroke (Tables 2 to 5). These biomarkers may be useful in assessing patients who are suspected of

having acute ischemic stroke, especially in the emergency service when thrombolytic treatment is being considered. A widely-used, rapid, and sensitive biomarker for acute ischemic stroke has not previously been available.¹¹ A specific biomarker that can be detected in blood in the early stages of stroke may facilitate accurate diagnosis in emergency situations, especially in smaller centers that do not have CT or MRI scanners available.

The ideal biomarker for acute ischemic stroke should increase in the early stage, rapidly diffuse into the blood circulation from the ischemic tissue, have a half-life of several hours, and be specific for ischemic nerve tissue.¹² Most (87%) acute strokes are caused by atherothrombotic events.¹³ Atherosclerosis, an important and preventable risk factor for acute ischemic stroke, develops after a long asymptomatic period, and the first sign of the presence of atherosclerosis may be an acute event such as myocardial infarction or stroke.^{7,14} Acute ischemic stroke is a preventable disease because risk factors and inhibitors are well described. Inflammation is important in the development of atherosclerosis that precedes an ischemic event.¹⁵ The studies conducted by using protein biomarkers in patients who have ischemic cerebrovascular disease are focused on pathophysiology, diagnosis,

Table 3 Relationship between level of consciousness rated by the Glasgow coma scale and outcome parameters in patients who had acute ischemic stroke

Parameter	Total	Mild	Moderate	Severe	P-value			
		15	8 to 14	3 to 7				
Glasgow coma scale	Number of patients	Number of patients	Number of patients	Number of patients				
Canadian neurological scale	102	76	9±2	22	6±3	4	0.4±0.4	0.001
Nonlacunar infarct volume (mL)	48	30	29±36	15	48±69	3	95±88	NS
Lacunar infarct volume (mL)	54	46	3±3	7	5±6	1	5.1	NS
hs-CRP (mg/dL)	200	166	3±5	28	7±7	6	8±6	0.001
Lp-PLA ₂ (nmol/min/mL)	200	166	134±71	28	126±75	6	172±39	NS

Notes: Data reported as number or mean ± standard deviation. Statistical significance was defined as $P \leq 0.05$.

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; Lp-PLA₂, lipoprotein-related phospholipase A₂; NS, not significant ($P > 0.05$).

Table 4 Relationship between high-sensitivity C-reactive protein level and infarct volume in patients who had acute ischemic stroke

Stroke type	Total	hs-CRP level (mg/dL)						P-value
		Low <3	Medium 3 to 15		High >15			
		Number of patients	Number of patients	Number of patients	Number of patients	Number of patients	Number of patients	
Nonlacunar infarct volume (mL)	48	13	8±9	25	55±65	10	43±37	0.04
Lacunar infarct volume (mL)	53	31	2±1	19	5±5	3	8±8	0.001

Notes: Data reported as number or mean ± standard deviation. Statistical significance was defined as $P \leq 0.05$.

Abbreviation: hs-CRP, high-sensitivity C-reactive protein.

and prognosis of stroke.¹⁶ Therefore, many biomarkers such as basal plasma brain natriuretic peptide, N-terminal probrain natriuretic peptide, cortisol, copeptin, D-dimer, interleukin 18 (IL-18), S100B, hs-CRP, and Lp-PLA₂ have been evaluated for utility in detecting acute ischemic stroke, but there is no globally accepted biomarker available.¹⁷⁻²²

Plasma D-dimer level is increased with higher National Institutes of Health stroke scale score and infarct volume.²⁰ Levels of IL-18 increase significantly in patients who have acute ischemic stroke, but there is no significant relationship between infarct volume and IL-18 level.^{17,23,24} In contrast, increase in S100B protein level is associated with increased infarct diameter and poorer prognosis.¹⁸

Previous studies showed that inflammatory indicators such as hs-CRP and proinflammatory cytokines are associated with early neurologic deterioration or poor functional results after stroke.^{25,26} Inflammatory processes likely contribute to cerebral ischemia, and ischemic brain damage is characterized by changes in acute local inflammation and inflammatory cytokines such as hs-CRP. Increased stroke risk is associated with increased hs-CRP levels. The acute phase protein CRP serves as a biological marker of systemic inflammation, and hs-CRP is associated with vascular inflammation. Increased hs-CRP levels are a predictive indicator of atherosclerosis and are associated with ischemic stroke.²⁷ In a previous study performed with patients who presented to the emergency service and were diagnosed with acute

ischemic stroke, increased hs-CRP levels were associated with an increase in ischemic volume.²⁸ Furthermore, risk of mortality is increased in patients who have hs-CRP levels increased within 72 hours after onset of acute ischemic stroke. In a long-term study (4-year follow-up) of patients who had acute ischemic stroke, increased hs-CRP levels were associated with increased mortality, but hs-CRP levels were not associated with recurrent acute ischemic stroke.⁹

During the inflammatory process, the intracellular phospholipase enzyme Lp-PLA₂ hydrolyzes the ester bonds of lipoproteins and oxidizes phospholipids on cell membranes. This enzyme causes the release of lysophosphatidylcholine, which has proinflammatory features by metabolizing low-density lipoprotein cholesterol.^{8,13} The level of Lp-PLA₂ may increase after ischemic events, and increased Lp-PLA₂ levels are associated with stroke in healthy middle-aged adults, healthy adults aged >55 years, and patients who have recurrent strokes.^{9,10,29} When a first stroke or strokes occur within 6 months after a transient ischemic attack, increased Lp-PLA₂ may be associated with recurrence of acute ischemic stroke but not mortality.^{9,30}

In the present study, we evaluated the relationship between serum hs-CRP level and Lp-PLA₂ activity, ischemic tissue volume, and severity of disease in patients who had acute ischemic stroke. Patients who had stroke had higher mean serum hs-CRP levels and Lp-PLA₂ activity than control patients who did not have stroke (Table 1). Further-

Table 5 Relationship between lipoprotein-related phospholipase A₂ activity and infarct volume in patients who had acute ischemic stroke

Stroke type	Total	Lp-PLA ₂ level (nmol/min/mL)					P-value	
		Low <100	Medium 100 to 150		High >150			
		Number of patients	Number of patients	Number of patients	Number of patients	Number of patients		
Nonlacunar infarct volume (mL)	48	12	4±5	8	31±40	28	57±60	0.01
Lacunar infarct volume (mL)	53	34	1±1	5	12±6	14	4±3	0.001

Notes: Data reported as number or mean ± standard deviation. Statistical significance was defined as $P \leq 0.05$.

Abbreviation: Lp-PLA₂, lipoprotein-related phospholipase A₂.

more, patients who had stroke had a significant relationship between hs-CRP level and Lp-PLA₂ activity, infarct volume, and stroke severity (Canadian neurological scale) (Table 2). Higher mean hs-CRP level was associated with lower level of consciousness (Glasgow coma scale) (Table 3). In addition, higher hs-CRP level and Lp-PLA₂ activity were associated with increased nonlacunar and lacunar infarct volumes (Table 4 and 5). Therefore, increased hs-CRP level and Lp-PLA₂ activity in stroke patients may be an indicator of poor prognosis. Although some studies showed that high hs-CRP levels in patients with ischemic stroke are associated with poor clinical outcomes, other studies have shown opposite findings.^{10,31} The present study confirmed the findings of other studies that showed an association between Canadian neurological system, Glasgow coma scale, and infarct volume; lower scores (indicating greater severity of neurologic impairment or level of consciousness) in patients who have acute ischemic stroke are associated with significant increase in infarct volume detected with diffusion-weighted imaging, duration of hospital stay, morbidity, and mortality.^{32–34} In the present study, decreased Canadian neurological scale scores were associated with increased nonlacunar and lacunar infarct volumes (Table 2). The finding that medium levels of Lp-PLA₂ were associated with the largest mean lacunar infarct volumes may have been caused by the small number of patients (five) who had medium Lp-PLA₂ levels and lacunar infarct (Table 5).

Limitations of the present study included the small sample size, especially when patients who had stroke were divided into subgroups according to stroke severity level. The stroke severity was determined by physical examination and infarct diameter, but long-term follow-up for morbidity and mortality was not performed; therefore, the association between hs-CRP level, Lp-PLA₂ activity, and morbidity and mortality was not assessed. In addition, ischemia volumes were measured in the diffusion-weighted magnetic resonance images obtained during the initial presentation of the patient, and increase in infarct size may have occurred subsequently. Nevertheless, the present results provide justification for future studies with more patients to evaluate the correlation between hs-CRP level, Lp-PLA₂ activity, and ischemia volumes noted on diffusion-weighted magnetic resonance images.

In summary, we detected a relationship between serum hs-CRP level and Lp-PLA₂ activity, ischemic tissue volume, and severity of acute ischemic stroke. Therefore, hs-CRP and Lp-PLA₂ may be useful as possible biomarkers for the diagnosis of acute ischemic stroke.

However, they probably will not replace CT or MRI because the latter provide anatomic information not available from a blood test. Further study is warranted to evaluate these biomarkers as possible convenient and cost-effective diagnostic studies for acute ischemic stroke.

Acknowledgment

This study was supported by Selçuk Üniversitesi Bilimsel Araştırma Projeleri Koordinatörlüğü.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Yoldas T, Gonen M, Godekmerdan A, Ilhan F, Bayram E. The serum high-sensitive C reactive protein and homocysteine levels to evaluate the prognosis of acute ischemic stroke. *Mediators Inflamm.* 2007;2007:15929.
2. Laskowitz DT, Kasner SE, Saver J, Rempel KS, Jauch EC; BRAIN Study Group. Clinical usefulness of a biomarker-based diagnostic test for acute stroke: the Biomarker Rapid Assessment in Ischemic Injury (BRAIN) study. *Stroke.* 2009;40(1):77–85.
3. Korkmaz I, Eren ŞH, Güven FM, Seğmen H. The clinical significance of multimarker index for early diagnosis among the patients admitted to the emergency department with suspected stroke. *Balkan Med J.* 2011;28(1):33–36.
4. Fiebach JB, Schellinger PD, Jansen O, et al. CT and diffusion-weighted MR imaging in randomized order: diffusion-weighted imaging results in higher accuracy and lower interrater variability in the diagnosis of hyperacute ischemic stroke. *Stroke.* 2002;33(9):2206–2210.
5. Krutzmann A, Köhrmann M, Sobesky J, et al. Pretreatment diffusion-weighted imaging lesion volume predicts favorable outcome after intravenous thrombolysis with tissue-type plasminogen activator in acute ischemic stroke. *Stroke.* 2011;42(5):1251–1254.
6. Katzan IL, Hammer MD, Hixson ED, et al; Cleveland Clinic Health System Stroke Quality Improvement Team. Utilization of intravenous tissue plasminogen activator for acute ischemic stroke. *Arch Neurol.* 2004;61(3):346–350.
7. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med.* 1999;340(2):115–126.
8. Lerman A, McConnell JP. Lipoprotein-associated phospholipase A₂: a risk marker or a risk factor? *Am J Cardiol.* 2008;101(12A):11F–22F.
9. Elkind MS, Tai W, Coates K, Paik MC, Sacco RL. High-sensitivity C-reactive protein, lipoprotein-associated phospholipase A₂, and outcome after ischemic stroke. *Arch Intern Med.* 2006;166(19):2073–2080.
10. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase A₂, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Arch Intern Med.* 2005;165(21):2479–2484.
11. Jensen MB, Chacon MR, Sattin JA, Levine RL, Vemuganti R. Potential biomarkers for the diagnosis of stroke. *Expert Rev Cardiovasc Ther.* 2009;7(4):389–393.
12. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther.* 2001;69(3):89–95.
13. Gorelick PB. Lipoprotein-associated phospholipase A₂ and risk of stroke. *Am J Cardiol.* 2008;101(12A):34F–40F.
14. Wildgruber M, Swirski FK, Zernecke A. Molecular imaging of inflammation in atherosclerosis. *Theranostics.* 2013;3(11):865–884.

15. Rost NS, Wolf PA, Kase CS, et al. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. *Stroke*. 2001;32(11):2575–2579.
16. Lynch JR, Blessing R, White WD, Grocott HP, Newman MF, Laskowitz DT. Novel diagnostic test for acute stroke. *Stroke*. 2004;35(1):57–63.
17. Zaremba J, Losy J. Interleukin-18 in acute ischaemic stroke patients. *Neurol Sci*. 2003;24(3):117–124.
18. Foerch C, Singer OC, Neumann-Haefelin T, du Mesnil de Rochemont R, Steinmetz H, Sitzer M. Evaluation of serum S100B as a surrogate marker for long-term outcome and infarct volume in acute middle cerebral artery infarction. *Arch Neurol*. 2005;62(7):1130–1134.
19. Tu WJ, Dong X, Zhao SJ, Yang DG, Chen H. Prognostic value of plasma neuroendocrine biomarkers in patients with acute ischaemic stroke. *J Neuroendocrinol*. 2013;25(9):771–778.
20. Zi WJ, Shuai J. Plasma D-dimer levels are associated with stroke subtypes and infarction volume in patients with acute ischemic stroke. *PLoS One*. 2014;9(1):e86465.
21. Barber M, Langhorne P, Rumley A, Lowe GD, Stott DJ. D-dimer predicts early clinical progression in ischemic stroke: confirmation using routine clinical assays. *Stroke*. 2006;37(4):1113–1115.
22. Montaner J, Perea-Gainza M, Delgado P, et al. Etiologic diagnosis of ischemic stroke subtypes with plasma biomarkers. *Stroke*. 2008;39(8):2280–2287.
23. Yamagami H, Kitagawa K, Hoshi T, et al. Associations of serum IL-18 levels with carotid intima-media thickness. *Arterioscler Thromb Vasc Biol*. 2005;25(7):1458–1462.
24. Gürkaş E, Orhan G, Ak F. [Association between interleukin-18 levels and early and late clinical findings and infarction volume in patients with acute ischemic stroke]. *Türk Beyin Damar Hastalıkları Dergisi*. 2012;18(1):10–15. Turkish.
25. Vila N, Castillo J, Dávalos A, Chamorro A. Proinflammatory cytokines and early neurological worsening in ischemic stroke. *Stroke*. 2000;31(10):2325–2329.
26. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336(14):973–979.
27. Khan A, Ali Z. Frequency of raised C-reactive protein in acute ischemic stroke. *Khyber Med Univ J*. 2012;4(2):45–48.
28. Youn CS, Choi SP, Kim SH, et al. Serum highly selective C-reactive protein concentration is associated with the volume of ischemic tissue in acute ischemic stroke. *Am J Emerg Med*. 2012;30(1):124–128.
29. Oei HH, van der Meer IM, Hofman A, et al. Lipoprotein-associated phospholipase A₂ activity is associated with risk of coronary heart disease and ischemic stroke: the Rotterdam Study. *Circulation*. 2005;111(5):570–575.
30. Furie KL, Parides MK, Greer DM, et al. Lipoprotein-associated phospholipase A₂ activity predicts early stroke recurrence [2007 International Stroke Conference abstract 20]. *Stroke*. 2007;38(2):458.
31. Winbeck K, Poppert H, Etgen T, Conrad B, Sander D. Prognostic relevance of early serial C-reactive protein measurements after first ischemic stroke. *Stroke*. 2002;33(10):2459–2464.
32. Wunderlich MT, Ebert AD, Kratz T, Goertler M, Jost S, Herrmann M. Early neurobehavioral outcome after stroke is related to release of neurobiochemical markers of brain damage. *Stroke*. 1999;30(6):1190–1195.
33. Sahan M, Sebe A, Acikalin A, et al. Acute-phase reactants and cytokines in ischemic stroke: do they have any relationship with short-term mortality? *Eur Rev Med Pharmacol Sci*. 2013;17(20):2773–2777.
34. Saposnik G, Kapral MK, Liu Y, et al; Investigators of the Registry of the Canadian Stroke Network; Stroke Outcomes Research Canada (SORCan) Working Group. IScore: a risk score to predict death early after hospitalization for an acute ischemic stroke. *Circulation*. 2011;123(7):739–749.

Neuropsychiatric Disease and Treatment

Publish your work in this journal

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the 'PsycINFO' database and CAS,

Submit your manuscript here: <http://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal>

Dovepress

and is the official journal of The International Neuropsychiatric Association (INA). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.