The study of significance of C reactive protein(CRP) and plasma fibrinogen as a predictors of in hospital mortality in 1st ever ischaemic stroke patients

***Dr Monem Makki Alshok** ***Dr Hassanain MS**

***Department of Medicine , College of Medicine , University of Babylon**

Correspondence to Address e:mail (dr_monem_alshok@yahoo.com)

Abstract

Background: There is increasing evidence that inflammation and hypercoagulability play an important role in the pathophysiology of acute ischaemic stroke. We evaluate in this prospective study the significance of C reactive protein(CRP) and plasma fibrinogen measured within 24 hours of stroke onset as a predictors of in hospital mortality in 1st ever ischaemic stroke patients and their correlations with stroke severity.

Methods: a total of 70 patients with 1st ever ischaemic stroke were included in the study. CRP and plasma fibrinogen was measured within 24 hours of stroke onset. Stroke severity was assessed by modified national institute of health stroke scale (mNIHSS) on admission and brain Computerized tomography (CT) scan was done for all patients within 48 hours of hospitalization. The patients were followed daily during the period of hospitalization. The end point was all causes of in hospital death or discharge from hospital.

Results: CRP and plasma fibrinogen were positively correlated with stroke severity (spearman correlation coefficient = 0.688 and 0.582 respectively). CRP and plasma fibrinogen were significantly associated with in hospital mortality after adjustment of sex, smoking, hypertension and diabetes.

Conclusion: CRP and plasma fibrinogen levels can predict independently the risk of in hospital death in 1st ever ischaemic stroke patients emphasizing the role of inflammation and coagulation in the evolution of ischaemic stroke. CRP and plasma fibrinogen correlate with stroke severity.

Key words: C reactive protein, plasma fibrinogen, ischaemic stroke.

Introduction

Stroke definition and epidemiology: The recommended World Health Organization stroke definition is "a rapidly developing clinical symptoms and or signs of focal (or global) disturbance of cerebral function, which lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin". [1, 2]A first-ever stroke means a stroke that occurs in a person who never had had a stroke before. [1]. Thus the definition of stroke is clinical, and laboratory investigations including brain imaging are used to support the diagnosis. [3] Stroke is a major public health problem, being the third most common cause of death after myocardial infarction and cancer, and the leading cause of adult disability. [1, 4, 5] There is mounting evidence that inflammation plays an important role in the pathophysiology of ischaemic stroke. [2, 6, 7]Cerebral ischaemia triggers a cascade of inflammatory events characterized by the activation and release of acute phase proteins such as C-reactive protein (CRP), and cytokines. Of the various inflammatory reported markers CRP is the best studied. [7]

Much recent scientific evidence has assigned to inflammation a fundamental role in pathogenesis of atherosclerosis in all stages of this disease: starting, progression and thrombotic complications. [8, 9, 10] CRP a peripheral marker of inflammation is also a marker of generalized atherosclerosis. [11, 12, 13, 14] It has been shown that CRP levels are an independent predictor of future cardiovascular events both in the general population and in the ischaemic stroke patients. [15, 16, 7]The recent JUPITER trial shows that the use of rosuvastatin in patients with high CRP has a significant impact both in reducing the CRP level and in lowering future vascular events. [17]This indicates the role of inflammation in atherogenesis and suggests that CRP can be used as marker of future vascular events. [14, 18, 19] However the role of CRP as a marker during and after ischaemic stroke is less extensively studied in comparison to coronary artery disease. [14]

Biology of CRP :

CRP is a trace protein in the circulation of healthy subjects. However, concentration can increase 100-fold or more in response to injury, infection, or inflammation. [20,21] CRP is produced mostly by liver hepatocytes in response to cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor. CRP is a member of the pentraxin protein family and comprises 5 identical protomers. It is not related to C-peptide or protein C. Apart from liver failure, there are no or few known factors that interfere with CRP production. [22] Various analytic methods are available for CRP determination, such as ELISA, immunoturbidimetry,

rapid immunodiffusion, and visual agglutination. Normal reference range for blood test is less than 5 mg/l (μg/ml). [23] There is also increasing evidence that activation of the coagulation system is associated with the development and evolution of acute ischaemic stroke. [7]

Biology & Pathophysiology of plasma fibrinogen:

Fibrinogen is a soluble glycoprotein found in the plasma, with a molecular weight of 340 kDa. As a clotting factor, fibrinogen is an essential component of the blood coagulation system, being the precursor of fibrin. However, at the 'usual' plasma levels of 150 to 450m g/dl, its concentration far exceeds the minimum concentration of 50 to 100 mg/dl necessary for hemostasis. Fibrinogen plays a vital role in a number of physiopathological processes in the body, including inflammation, atherogenesis and thrombogenesis. Nevertheless, our understanding of the mechanisms leading to the atherothrombogenic action of fibrinogen is fragmentary. Proposed mechanisms include the infiltration of the vessel wall by fibrinogen, haemorrheological effects due to increase in blood viscosity, increased platelet aggregation and thrombus formation. Furthermore, plasma fibrinogen is also a prominent acute-phase reactant. It augments the degranulation of platelets in response to adenosine diphosphate (ADP), when taken up by the alpha granules. [28] Elevated levels of fibrinogen have been associated with future cardiovascular event in healthy individuals, [29] have been reported after stroke, [30] and have been associated with increased risk of recurrent stroke. [31, 32, 7]However the influence of plasma fibrinogen levels at stroke onset on outcome from stroke is not as well studied. [33]

Most studies, however, have reported on long term prognostic value of various inflammatory and haemostatic markers in ischaemic stroke patients and there is very limited information concerning their in hospital prognostic value. [7]

Aims of the study

1. Evaluate the significance of CRP and plasma fibrinogen measured within 24 hours of stroke onset as predictors of in hospital mortality of ischaemic stroke and their independent contribution on mortality.
2. Correlate between CRP, plasma fibrinogen and stroke severity.

Materials and methods

Subjects : We conduct an observational prospective study on 70 patients with 1st ever ischaemic stroke admitted to Merjan teaching hospital from the 15th of April 2009 to 1st of July 2009 and to the medical city hospital from the 1st of August 2009 to the 1st of October 2009.

Exclusion criteria : Patients were excluded from the study if they had history of previous stroke, atrial fibrillation, chronic renal failure, chronic liver disease, chronic inflammatory disease, malignancy, surgery or trauma in the previous month, obvious symptom or clinical signs of infection at time of hospital admission, time interval more than 24 hours between the onset of symptoms and the venous sampling, ESR more than 30, age below 45 and above 65 years, uses of NSAID except aspirin, use of corticosteroid, pregnancy, vascular events e.g. myocardial infarction and deep vein thrombosis during the last 6 weeks, Patients who were discharged before the 4th day of hospitalization were also excluded from the study. Similarly Patients with transient ischaemic attack and hemorrhagic stroke were also excluded from the study.

Stroke was defined according to world health organization stroke definition criteria. [1, 2] The diagnosis of acute ischaemic stroke was established both clinically and radiologically (CT scan was done for all patients within 48 hours of hospital admission which show infarction or absence of hemorrhage). Stroke onset was defined as time of onset of symptom or the last time the patient was seen to be normal. [1]

Potential risk factor for cerebrovascular disease including hypertension(HPT), diabetes(DM), smoking, ischaemic heart disease as well as age of the patients, use of antiplatelets prior to hospital admission and other information was reviewed by direct questionnaire to the patients or their relatives. Risk factors were defined according to protocol. Patients with a history of HPT or without a history but who had blood pressure reading equal or more than 140/90 mm Hg were defined hypertensive.[3] Patients who have history of DM, being on glucose lowering medication prior to stroke onset or without a history but who had fasting blood sugar more than 126 mg/dL on 2 occasions were defined diabetics. [3] Patients were regarded as current smokers if they smoked until admission or stopped smoking within the last 3 months. [7] All patients had general examination, assessment of the vital signs, full neurological examination and 12 leads electrocardiogram (ECG) on admission. Stroke severity on admission was assessed by mNIHSS; the mNIHSS is an 11-item quantitative scale of stroke-related neurologic deficit and it is considered simpler and at least equally reliable and valid with the standard national institute of health stroke scale (NIHSS).[7,34] Minimum score is 0 and maximum score is 32.

Blood sampling and laboratory methods: Venous blood was drawn on admission at the time of inserting intravenous line. The blood divided into two samples. The first sample collected into a tube containing sodium citrate and send for plasma fibrinogen immediately. The second sample

collected into a plain tube, allowed to clot and then separate the serum by centrifuging the sample and stored at 2-8 Celsius for few days for measurement of CRP and the remaining serum used to measure blood sugar, blood urea, and serum creatinine. Serum CRP level was measured using ELISA technique (enzyme linked immunosorbent assay)using DRG® C- reactive protein (CRP) ELISA (EIA-1952), an enzyme immunoassays for the quantitative determination of CRP in human serum and plasma. The minimal detectable concentration is 1 µg/ml. Plasma fibrinogen was measured using dry clot weight method. [35] General urine examination, chest x ray and blood film were done in some patients according to the clinical situation to exclude concurrent infections.

Statistical analyses: Normally distributed variables are presented as mean ± standard deviation (SD) such as the age of the patients, duration of hospitalization and time between onset of symptoms and venous sampling. Because of their skew distributions, CRP and plasma fibrinogen presented as medians and tertiles. For CRP we take an arbitrary cut off points of 25 and 100 µg/ml which correspond approximately to the median and upper 20 % distribution (80^{th} centile) to divide the sample into 3 groups, namely 1^{st}, 2nd and 3^{rd} tertiles.

The 1^{st} tertile includes CRP values between 1 and 25µg/ml, 2^{nd} tertile includes CRP values from 26 to 99µg/ml and the 3^{rd} tertlie include CRP values from 100 to 140µg/ml.

The same principles were applied to plasma fibrinogen with cutoff points of 190 mg/dl and 390mg/dl which correspond approximately to the median and upper 20% distribution. Correspondingly the 1^{st}tertile includes plasma fibrinogen values from 150 to 190 mg/ dL, 2^{nd} tertile includes plasma fibrinogen values from 191 to 390 mg/ dL and the 3^{rd} tertile contain plasma fibrinogen values from 391 to 490 mg/ dL. Correlations between continuous variables which were not normally distributed; CRP levels, plasma fibrinogen, and stroke severity measured by mNIHSS were assessed using nonparametric spearman correlation coefficient. Associations between categorical variables (CRP tertiles, plasma fibrinogen tertiles, death, HPT, DM, sex and smoking) were tested by the use of chi-square fisher exact test. In order to evaluate the independent contribution of CRP and plasma fibrinogen on in hospital mortality, binary logistic regression models were applied, with HPT ,DM, sex and smoking as possible confounding factors with forward LR (likelihood ratio) entry is applied to the model.

Because of colinearity, CRP and plasma fibrinogen does not enter the same model. P value of 0.05 or less was considered significant. Statistical analysis was performed using SPSS version.

Results

A total of 70 patients were included in our study. Age of the patients ranged from 45 to 65 years (mean 54.74±5.115). 42 patients were male and 28 were female (male to female ratio equal to 1.5). 30 patients were smoker (42.85%), 32 patients were hypertensive (45.71%), 24 patients were diabetics (34.28%), 17 patients had history of ischaemic heart disease (24.28 %), 19 patients reported the use of antiplatelets prior to stroke onset (27.14%), 12 patients were taking antiplatelets for preexisting ischaemic heart disease and 5 patients were taking antiplatelets for secondary prevention for another associated risk factor. Eight patients died during hospitalization (11.42%).Time between stroke onset and venous sampling ranged from 2 to 22 hours (mean 9.39 ± 4.338). Duration of hospitalization ranged from 4 to14 days (mean5.34 ± 1.45). Death occurred after a mean of (5.555 ± 3.431) days.

Tables 1: shows the correlation between baseline patients' characteristics and in- hospital mortality. There was a significant correlation between DM, HPT and in hospital mortality. While there was no significant correlation between sex, smoking, history of IHD, use of antiplatelets prior to stroke onset and the in hospital mortality.

Table 2: shows the correlation between CRP, plasma fibrinogen and stroke severity assessed by mNIHSS. CRP positively correlated with plasma fibrinogen (rho = 0.815), and mNIHSS (rho= 0 .688). Similarly plasma fibrinogen positively correlated with mNIHSS (rho =0 .582).

Tables 3: shows the correlation between CRP and in hospital mortality. In the 1st tertile (35pateints) only one patient died (2.9%), in the 2nd tertile (21 patients) also one patient died (4.8%), however in the 3rd tertile (14 patients) six patients died (42.9%). There was a significant correlation between CRP and in hospital mortality (P value 0.001).

Tables 4: demonstrates the correlation between plasma fibrinogen and in hospital mortality. In the 1st tertile (35 patients) only one patient died (2.9%). In the 2ndtertile (14 patients) 2 patients died (9.5%), and in the 3rd tertile (14 patients) 5 patients died (35.7%). This correlation was statistically significant (p value 0.006).

Table 5: shows the result of logistic regression analysis for CRP model. The outcome or dependent variable was the in hospital mortality and the independent variables or confounding factors were HPT, DM, sex, smoking and CRP levels. Smoking and sex were excluded from the equation by the model because their addition or removal does not alter the model significantly.

The adjusted odds ratio for CRP was 1.344, which mean that the odd of death increased by 1.344 for each 10 μg/ml increment of CRP levels provided that DM, HPT, sex, and smoking were equal. So CRP was significantly correlated with in hospital mortality after adjustment of HPT, DM, sex and smoking.

Table 6; shows the result of logistic regression analysis for plasma fibrinogen model. The outcome or dependent variable was the in hospital mortality and the independent variables or confounding factors were HPT, DM, sex, smoking and plasma fibrinogen levels. Similarly sex and smoking were excluded by the model. The adjusted odds ratio for plasma fibrinogen was 1.901, which means that the odd of death increased by 1.901for each 50 mg/dL increment of plasma fibrinogen provided that DM, HPT, sex, and smoking were equal. So plasma fibrinogen was significantly correlated with in hospital mortality of ischaemic stroke after adjustment of HPT, DM, sex and smoking.

Table 1Correlation between Baseline patients' characteristics and in hospital mortality

Patients characteristics		Mortality		total		P value
		Death(8)	Survival (62)			
Sex	Male	6 75%	36 58.1%	42	70	0.624
	female	2 25%	26 41.9	28		
DM	yes	6 75%	18 29.9%	24	70	0.017
	no	2 25%	44 70.1%	46		
HPT	yes	7 87.5%	25 40.3%	32	70	0.020
	no	1 12.5%	37 59.7%	38		
Smoking	yes	6 75 %	24 38.7 %	30	70	0.066
	no	2 25%	38 61.3%	40		
Antiplatelet use	yes	4 50%	15 24.2%	19	70	0.200

	no	4 50%	47 75.8%	51		
IHD	yes	4 50%	13 21%	17	70	0.092
	no	4 50%	49 79%	53		

Table 2 Correlation between CRP, plasma fibrinogen and stroke severity assessed by mNIHSS

Variable	variable	Spearman correlation coefficient
CRP	Plasma fibrinogen	0.815
CRP	mNIHSS	0.688
Plasma fibrinogen	mNIHSS	0.582

Table 3 Correlation between CRP and in hospital mortality

In hospital mortality	CRP			total
	1st tertile	2nd tertile	3rd tertile	
Death No. %	1 2.9%	1 4.8%	6 42.9%	8
Survival No. %	34 97.1%	20 95.2%	8 57.1%	62
Total	35	21	14	70

P value 0.001

Table 4 Correlation between plasma fibrinogen and in hospital mortality

In hospital mortality	Plasma fibrinogen			total
	1st tertile	2nd tertile	3rd tertile	
Death No. %	1 2.9%	2 9.5%	5 35.7%	8
Survival No. %	34 97.1%	19 90.5%	9 64.3%	62
Total	35	21	14	70

P value 0.006

Table 5 The adjusted and unadjusted association of independent variables with in- hospital death according to the result of logistic regression analysis of CRP model

Independent variable	unadjusted			Adjusted		
	P value	OR	CI	P value	OR	CI
CRP*	**0.002**	**1.332**	**1.113–1.595**	**0.010**	**1.344**	**1.074 – 1.681**
HPT	**0.034**	**10.360**	**1.200 – 89.462**	**0.061**	**11.074**	**0.898 – 136.572**
DM	0.021	7.333	1.351– 39.809	0.024	12.943	1.391 – 120.449

***Per 10 µg/ml increment**.

Table 6 The adjusted and unadjusted association of independent variables and in hospital death according to the results of logistic regression analysis of plasma fibrinogen model

Independent variable	unadjusted			adjusted		
	P value	**OR**	**CI**	**P value**	**OR**	**CI**
Fibrinogen *	**0.013**	**1.662**	**1.115 – 2.477**	**0.022**	**1.904**	**1.099 – 3.300**
HPT	**0.034**	**10.360**	**1.200–89.462**	**0.018**	**25.202**	**1.724–368.354**
DM	0.021	7.333	1.351–39.809	0.032	9.058	1.210–67.835

***Per 50mg/dL increment.**

Discussion:

We adopted strict criteria for enrolment in order to form a rather homogeneous group.

First, we did not include patients more than 65 years. This limited the effect of co-morbid conditions more prevalent in elderly patients, such as infections, possibly unrecognized on admission that could influence the inflammatory status. Patients below 45 years also excluded because the stroke aetiology in such patients is different and such entity is called stroke in young. We also tried to exclude as much as possible patients with comorbid conditions that might affect CRP and/or plasma fibrinogen levels.

Second, the short period of blood intake after symptom onset (mean = 9.39 h) almost ruled out the possibility that a non-neurological complication (urinary tract infection, deep vein thrombosis and so on) could have affected the levels of the studied markers.

Finally, we excluded patients with atrial fibrillation and those with hemorrhagic stroke. Therefore, the selected patients was more likely to have an underlying pathogenetic mechanism, the rupture of unstable atheromatous plaque in extracranial or intracranial arteries leading to atherothrombotic occlusion either by embolization of plaque material to distal cerebral arteries or by in situ occlusion, respectively.

Based on the data obtained from 70 patients involved in our cohort study; eight patients died during hospitalization (11.4 %).

This study showed significant correlation between admission CRP levels and stroke severity assessed by mNIHSS on admission (rho=0.688). L. S. Rallidis et al study showed a high colinearity between CRP levels and mNIHSS spearman correlation coefficient (rho=0.81). [7]

Other studies showed similar correlation using different neurological stroke scales. Titto T Idicula et al study reported that Stroke severity was associated with admission CRP levels even after adjusting for age, sex, intravenous thrombolysis and the presence of DM. stroke severity in this was assessed using national institute of health stroke scale (NIHSS).[14]

Another study showed that high sensitivity CRP on admission showed an increased trend with stroke severity measured by national institute of health stroke scale (NIHSS) with p value 0.033.[40]

The association between high CRP and stroke severity remains unexplained. There is a distinct possibility that elevated CRP is a direct response to the extent of cerebral tissue injury [41] but as an inflammatory marker, it is also possible that high CRP is associated with underlying processes that cause a more severe stroke. [14] Whether high CRP causes more severe stroke or vice versa needs to be further studied in population based larger cohort study.

This study showed significant correlation between admission CRP levels and in-hospital mortality in patients with 1st ever acute ischaemic stroke(p value 0.001) and the correlation continued to be significant after adjustment of HPT, DM, sex and smoking (OR = 1.344; 95% CI, 1.074 – 1.681; P value = 0.014 per10 μg/ml increments in CRP levels).

There are very few and conflicting data regarding the short-term prognostic value of CRP in ischaemic stroke patient. [7] Masotti et al study reported that elevated CRP levels within 12 h from admission were associated with 30-day mortality in very old patients (more than75 years) with acute ischaemic stroke. Mean values of CRP were significantly higher in patients who died in the first 30 days from stroke compared with survivors (10.7 vs. 4.3 mg ⁄ dL, P value = 0.0106).[10.] L. S. Rallidis et al study showed that CRP measured on admission were important predictors of in hospital mortality in middle-aged patients with 1st ever acute ischaemic stroke, and the association was independent on other cardiovascular risk factors. (OR =1.20; CI, 1.09–1.30; P value=<0.001 per 1 mg⁄ L). [7] Another study also showed that serum concentrations of CRP measured within 12 hours from admission were significantly higher in patients who died

during hospitalization compared with those who survived and were independently associated with early death, after adjusting for various confounding factors. For one unit increase in CRP, 14% higher risk of dying during hospitalization. [36] While another study; Canova CR et al failed to demonstrate an association of admission CRP levels with in hospital prognosis in stroke patients. [37]

There are plausible mechanisms through which CRP could be implicated with worse prognosis in acute stroke patients. Increased CRP may reflect a greater extent of brain necrosis [38] and a greater amount and activity of proinflammatory cytokines, which may potentiate ischaemic brain injury with several mechanisms such as upregulation of adhesion molecules, recruitment and activation of leukocytes and promotion of local procoagulant state. [7] In addition, CRP may potentiate brain damage by activating the complement system in atherosclerotic plaques leading to further plaque instability. [39] However CRP values are higher in ischaemic stroke than in TIA and in hemorrhagic stroke than in ischaemic stroke. This fact could reflect that CRP is a marker of local severity of brain attack. [10]

This study also showed that Plasma fibrinogen levels on admission were significantly associated with stroke severity (mNIHSS); spearman correlation coefficient ratio = 0.582.

L. S. Rallidis et al study also show high colinearity between plasma fibrinogen levels on admission and stroke severity measured by mNIHSS (rho = 0.95). [7]

This study showed that higher plasma fibrinogen levels on admission significantly associated with in hospital mortality (p value 0.006). After adjustment of HPT, DM, sex and smoking fibrinogen levels continued to be associated with mortality (OR =1.901; 95% CI, 1.099 – 3.300; P value = 0.022 per 50 /dl increments in plasma fibrinogen levels).

L. S. Rallidis et al study showed that that fibrinogen levels could, independently of other confounding factors, predict in hospital mortality in acute ischaemic stroke patients. (OR 1.18; 95% CI, 1.08 – 1.14; p value <0.001 per 10 mg/dl increment of plasma fibrinogen).

Tanne et al study reported that placebo patients who not receive thrombolytic therapy in the NINDS study with higher 24-hour fibrinogen levels were associated with approximately 40% increase in the odd of death by 90-day mortality (OR 1.42; 95% CI, 1.05 to 1.91 per 100 mg/dl increment; n 545).[42]

In contrast to our study, Beg M, Nizami A et al study showed that; after adjustment for other possible ischemic stroke risk factors; plasma fibrinogen levels was found to be still significantly

high in patients as compared to controls ($p<0.001$). Mean plasma fibrinogen level between patients who survived and who expired after 30 days did not differ significantly. [43]

The pathophysiological basis for the association of fibrinogen with early outcome is largely uncertain. Fibrinogen, similar to CRP, is an acute-phase reactant, as it is in addition a key factor in the coagulation cascade. Therefore, increased fibrinogen levels reflect an excess inflammatory response which is directly related to the extent of ischaemic area. In addition, high fibrinogen levels are indicative of a hypercoagulant response which may potentiate ischaemic brain injury by enhancing the atherothrombotic process in the involved cerebral artery. [7]

Finally this study showed a significant correlation between CRP and plasma fibrinogen level; spearman correlation coefficient rho= 0.815. This agrees with other studies. [44, 45]

Limitations of the study:

1. Although the applied inclusion criteria formed a group of stroke patients most likely suffered from an atherothrombotic event, other pathogenetic mechanisms of stroke cannot be excluded, such as paradoxical embolism through a patent foramen ovale.
2. we did not perform serial measurements for CRP. it has been reported that it peaks 36–48 h after stroke onset and therefore by collecting blood within 24 hours of stroke onset we probably obtained submaximal levels. However, even these submaximal levels had an independent impact on outcome.

In Conclusions:

1. CRP and plasma fibrinogen levels measured with in 24 of stroke onset correlate with in hospital mortality of 1st ever ischaemic stroke patients and are independent on HPT, DM and sex and smoking.
2. CRP and plasma fibrinogen levels significantly correlate with stroke severity.
3. This association emphasizes the role of inflammation and coagulation in the evolution of ischaemic stroke.
4. We can consider CRP and plasma fibrinogen as a red flag marker for in-hospital mortality of ischaemic stroke, but unfortunately therapeutic implication for this finding is not available at time being.

Recommendations

1.Since stroke is one of the main health problem worldwide and because of its higher mortality and disability, it is very important to address patients with high risk of adverse outcome.

2. We recommend measurement of CRP and plasma fibrinogen in all patients with acute ischaemic stroke as a marker of adverse outcome.

3.A further study is required to assess the significance of serial measurement of CRP and does CRP and plasma fibrinogen can be used to select patient as a candidate for new therapeutic intervention that might become available in our country in the future like trend of thrombolytic therapy for acute ischaemic stroke.

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