Relationship between Ankle Brachial Index (ABI), High Sensitivity C-Reactive Protein (hs-CRP) and Initial Disability Level in Acute Ischemic Stroke

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Background: *Relationship between high sensitivity C-reactive protein (hs-CRP), Ankle Brachial index (ABI), severity of atherosclerosis and risk of ischemic stroke has been well documented. Studies concerning the association of ABI, hs-CRP and initial disability level in acute ischemic stroke are scarce.*

Objective: *This study aimed to investigate the relationship between hs-CRP, ABI and level of initial disability in acute stroke setting.*

Material and Method: *We conducted a prospective observational study in patients with acute ischemic stroke within 48 hours of onset. Initial ABI, hs-CRP were measured. Disability level was assessed at admission and 3 months using the modified Rankin scale (mRS) and the National Institue of Health Stroke scale (NIHSS). Statistical analysis was performed using Pearson's correlation coefficient.*

Results: *This study included 36 patients with a mean $\pm$ SD age of 67.8 $\pm$ 9.3 years. Sixteen (44.4%) were male. Median NIHSS and mRS were 10 and 4 respectively. Correlation between initial ABI and hs-CRP was poor (r_s=-0.11, p= 0.57). There was a significant negative relationship between ABI and mRS at 0 and 3 months with a correlation coefficient of -0.45 (p = 0.006) and -0.41 (p = 0.02), respectively.*

Conclusion: *There was a significant inverse relationship between ABI and initial stroke disability. However, correlation coefficient indicated only fair agreement beyond chance. This findings suggest that ABI may be used as a clinical predictor of initial disability level in acute stroke.*

Keywords : *Acute ischemic stroke, Ankle brachial index (ABI), High sensitivity C-reactive protein (hs-CRP), modified Rankin scale (mRS)*

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C-reactive protein (CRP) is an acute phase response protein produced by hepatocytes following an acute injury or an inflammation. Its level reaches the peak at 50 hours, and gradually declines within 6 hours after the onset. The relationship between CRP level, atherosclerotic plaque burden and area of cerebral infarction has been demonstrated[1,2]. In addition, CRP level predicts recurrent ischemic stroke and the chance of post stroke recovery[3-8, 15].

Ankle Brachial Index (ABI) is a ratio between systolic blood pressure of Dorsalis pedis or Posterior tibial and Brachial artery. It is measured by a simple and non-invasive technique using a widely available portable ultrasound device. ABI indicates vessel wall laxity and elasticity. Several studies showed that patients with ABI of d"0.90 have a higher risk of ischemic stroke[9-11]. However, it is not known whether ABI and/or CRP can reliably predict initial stroke severity and disability level in acute stroke patients. This study aimed to assess the relationship between ABI, CRP and initial disability level in acute stroke setting.

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Objective

The goal of this study was to investigate the relationship between ABI, CRP and initial disability in acute ischemic stroke patients.

Material and Method

Participants were recruited from a consecutive series of acute ischemic stroke patients presented within

48 hours of symptoms onset. All patients were treated according to standard acute stroke treatment protocol including aspirin administration within 48 hours, intravenous thrombolysis, stroke unit admission and bedside early rehabilitation at the Siriraj Acute Stroke Unit, Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand. Patients with atrial fibrillation (AF), valvular heart disease, fever, and systemic or local inflammatory conditions were excluded. Demographic data, vital signs, initial disability level as measured by modified Rankin Score (mRS) and the National Institute of Health Stroke Scale (NIHSS) were recorded. Blood test for hs-CRP and measurement of ABI were performed within 48 hours after stroke onset. ABI assessment was done after a 5-minute rest in supine position using an 8 MHz probe, Nicolet Elite 100 Doppler ultrasound device and Aston manual aneroid sphygmomanometer. As for blood pressure measurement technique, the ultrasound head was placed at the loudest arterial signals. Blood pressure cuff was inflated until reaching the point of 30 mmHg after the signal diminished and then deflated at a rate of 2 mm Hg/second. The same measurement was performed three times and the highest systolic blood pressure (SBP) from each side was recorded for ABI calculation. Dorsalis pedis and Posterior tibialis pressure were measured using the same instruments and techniques. The cuff was placed at 1 inch above ankle joint line (the connection line between medial and lateral malleolus). The highest SBP measured from Dorsalis pedis and Posterior tibial artery of each side was used for calculation. The right and left ABI were calculated separately. The lowest value was then selected for statistical analysis. Patients were followed up at 3 months. Telephone follow-up was allowed if the patients were not available for a routine follow-up schedule. The study protocol was approved by Ethic Committee of the Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand.

Sample size calculation and statistical analysis

Approximately 30 stroke patients were needed to achieve 80% power with a Pearson's correlation coefficient between ABI, hs-CRP and mRS of 0.50. A 20% loss to follow up compensation were expected which resulted in a total number of 36 patients.

Categorical variables were presented as numbers and percentages. Continuous variables presented by mean □ SD and median. The relationships between hs-CRP, ABI and initial disability level were analyzed by Spearman 's rank correlation. Pearson's correlation was used if data were normally distributed. All tests performed were two sided and statistical significant was considered at a p-value of ≤ 0.05.

Results

Thirty-six patients were included in the study. Sixteen (44.4%) were male. Mean (SD) age was 67.8 (9.3) years. Diabetes, hypertension and dyslipidemia were documented in 38.9, 66.7 and 22.2% respectively. There was no prior stroke in 29 patients (80.6%). Median NIHSS were 10. Median mRS was 4. Median hs-CRP level was 2.54 mg/L (0-137). Mean (SD) ABI was 1 (0.3).

At the end of the study, 6 patients died. Two patients had intracerebral hemorrhage associated with intravenous thrombolysis. Four deaths were related to severe infection. There was a case of repeated ischemic stroke during the first three months.

There was a significant negative correlation between ABI and mRS at 0 and 3 months with a correlation of -0.45 ($p = 0.006$) and -0.43 ($p = 0.015$) respectively (Fig. 1, 2). Fig. 3 demonstrated a significant inverse relationship between ABI and NIHSS ($r = -0.36$, $p = 0.03$). There was no significant association between ABI and hs-CRP at arrival (correlation coefficient of -0.11, $p = 0.58$).

Discussion

Our study showed a fair inverse relationship between ABI, initial and 3-month disability level. A significant negative relationship was also found between ABI and initial stroke severity when measured

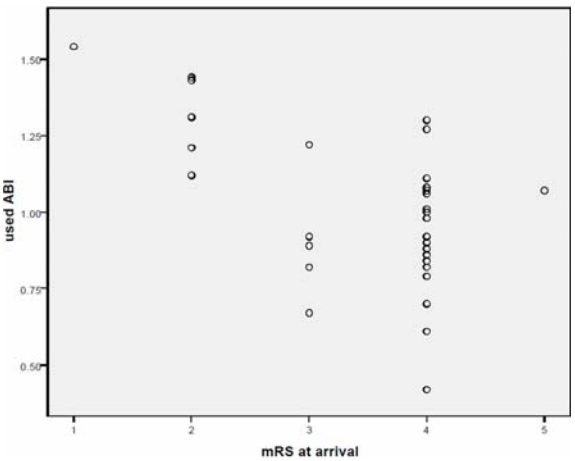

Fig. 1 Relationship between ABI and initial disability level as measured by mRS Spearman's rank correlation, $r_s = -0.45$ ($p = 0.006$)

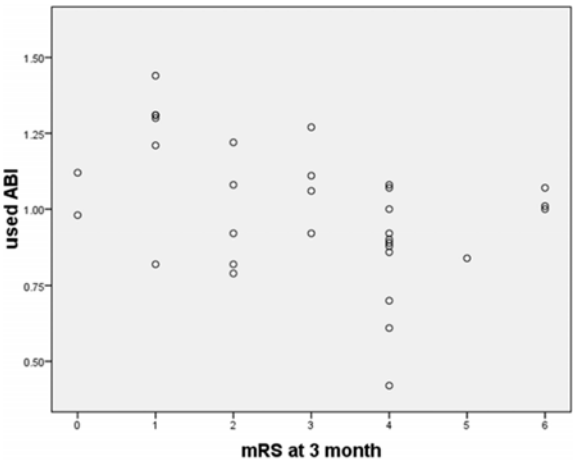

Fig. 2 Relationship between ABI and mRS at 3 months after stroke onset Spearman's rank correlation, r_s = -0.43 (p = 0.015)

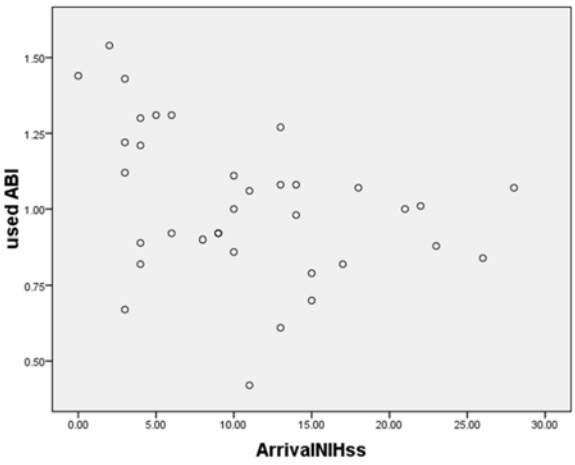

Fig. 3 Relationship between ABI and initial stroke severity as measured by NIHSS Pearson's correlation coefficient, r = -0.36 (p = 0.03)

by NIHSS. However, there was no association between hs-CRP and ABI in acute ischemic stroke setting.

A strong association between low ABI and an increase risk of ischemic stroke was demonstrated in a population-based study[9]. In addition, several studies have confirmed that patients with ABI of d" 0.90 have a higher risk of ischemic stroke [9-12]. Our study has provided additional information that if stroke occurred in a patient with low ABI, it tends to be more severe and associates with a poor outcome at three months. An explanation for these findings is that atherosclerotic change resulted in a reduction of ischemic vasoreactivity which may associate with poor

Table 1. Demographic data

Demographic data	Number
Age (years, Mean ± SD)	67.83 ± 9.30
Male (%)	16 (44.4)
Diabetic mellitus (%)	14 (38.9)
Hypertension (%)	24 (66.7)
Ischemic heart disease and/or peripheral arterial disease (%)	4 (11.1)
Previous history of stroke (%)	7 (19.4)
Dyslipidemia (%)	8 (22.2)
Current smoking (%)	12 (33.5)
Current alcohol drinking (%)	12 (33.5)
hs-CRP (mg/L, Median (min-max))**	2.54 (0-137)
ABI+ (Mean ± SD)	1 ± 0.3

**Six out of 36 patients developed fever before hs-CRP sampling. The mean value of hs-CRP was obtained from the remaining 30 patients.

+ One out of thirty six patients was excluded from ABI value calculation because of unobtainable ABI measurement which was due to severe hemodynamic alteration and critical illness.

collateral cerebral circulation[13,14]. Therefore, those with low ABI are likely to have low cerebral perfusion and result in more severe stroke and hence poor functional recovery.

There were certain limitations in our study. Firstly, ABI measurement was operator dependent. Reliability of ABI depends on examiner's clinical skills and measurement protocol. In our study, all patients were measured within the first week after the stroke onset by one neurologist (SC) who strictly followed the same protocol. In addition, a practice session was finished prior to the initiation of the study. In routine clinical practice, it is recommended for clinicians to follow a precise protocol in order to get a reliable measurement. Secondly, some of the study patients received intravenous tissue plasminogen activator (t-PA) which may affect the outcome. For example, an acute ischemic stroke patient with a low ABI who received t-PA might have better outcome when comparing to the high ABI patient who did not receive this medication. Therefore, the association between ABI and 3-month functional recovery might be affected by this intervention. Thirdly, there were some differences in post stroke rehabilitation program among study patients especially after being discharged. Some patients might receive intensive physical therapy whereas others received routine rehabilitation program.

Finally, this study involved small sample size. Thus, the findings need to be confirmed in a larger cohort study.

The findings from our study may have a practical impact on clinical practice since the ABI can be use as a simple mean to predict stroke risk, initial stroke severity, disability level and a short term functional recovery. Furthermore, ABI can be reliably measured by a simple and non-invasive ultrasound device which is widely available in many community hospitals or clinics. Therefore, this information can be retrieved and utilized by general practitioners, as well as neurologists, to emphasize the importance of stroke prevention strategies; for example, a physician can stress that if the patients have low ABI, they will not only have a higher risk of stroke but also will likely have more severe stroke and are less likely to have a good recovery. This may help the patients realize their cardiovascular risk status and adjust their lifestyles more appropriately.

In conclusion, our study demonstrated a significant inverse relationship between ABI and initial and stroke disability at 3 months. However, correlation coefficient indicated only fair agreement beyond chance. These findings may be used as a simple means for general practitioners, as well as neurologists, in predicting initial stroke disability and a short term recovery.

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Potential conflicts of Interest

None.

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ความสัมพันธ์ระหว่าง Ankle Brachial Index (ABI), high sensitivity C-Reactive Protein (hs-CRP) และระดับการสูญเสียความสามารถเบื้องต้นในผู้ป่วยโรคหลอดเลือดสมองตีบหรืออุดตันเฉียบพลัน

สงคราม โชติกอนุชิต, ยงชัย นิละนนท์, นิพนธ์ พวงวรินทร์

ภูมิหลัง: *หลักฐานการศึกษาแสดงถึงความสัมพันธ์ระหว่าง high sensitivity C-Reactive Protein (hs-CRP) Ankle Brachial Index (ABI) ความรุนแรงของโรคหลอดเลือดแดงแข็ง และความเสี่ยงของการเกิดโรคหลอดเลือดสมองตีบหรืออุดตัน แต่ยังไม่มีข้อมูลเพียงพอที่บ่งถึงความสัมพันธ์ระหว่าง ABI, hs-CRP และระดับการสูญเสียความสามารถเบื้องต้นเมื่อเกิดภาวะสมองขาดเลือดเฉียบพลัน*

วัตถุประสงค์: *เพื่อศึกษาความสัมพันธ์ระหว่าง hs-CRP, ABI และระดับการสูญเสียความสามารถเบื้องต้นในผู้ป่วยโรคหลอดเลือดสมองตีบหรืออุดตันเฉียบพลัน*

วัสดุและวิธีการ: *เป็นการศึกษาแบบติดตามไปข้างหน้าโดยผู้ป่วยโรคหลอดเลือดสมองตีบหรืออุดตันเฉียบพลันที่มีอาการภายใน 48 ชั่วโมงแรกจะได้รับการเจาะเลือดตรวจ hs-CRP วัดระดับค่า ABI พร้อมกับตรวจระดับการสูญเสียความสามารถเบื้องต้นโดยใช้ modified Rankin Scale (mRS) และ National Institute of Heath Stroke Score (NIHSS) เมื่อแรกรับและที่ 3 เดือน ประมวลผลทางสถิติด้วยค่าสัมประสิทธิ์สหสัมพันธ์เพียร์สัน และค่าสหสัมพันธ์แบบสเปียร์แมน*

ผลการศึกษา: *มีผู้ป่วยเข้าร่วมการศึกษาจำนวน 36 ราย อายุเฉลี่ย 67.8 ± 9.3 ปี เป็นเพศชาย 44.4% คะแนน NIHSS และ mRS มีค่ามัธยฐานเท่ากับ 10 และ 4 ตามลำดับ ผลการประมวลผลทางสถิติพบว่า ค่า ABI สัมพันธ์แบบผกผันอย่างมีนัยสำคัญทางสถิติกับ mRS แรกรับ (ค่าสัมประสิทธิ์สหสัมพันธ์ -0.45, p = 0.006) และที่ 3 เดือน (ค่าสัมประสิทธิ์สหสัมพันธ์ -0.41, p = 0.02) แต่ไม่พบความสัมพันธ์ทางสถิติระหว่างค่า ABI และ hs-CRP*

สรุป: *ค่า ABI สัมพันธ์กับระดับการสูญเสียความสามารถเบื้องต้น เมื่อเกิดโรคหลอดเลือดสมองตีบหรืออุดตันเฉียบพลันอย่างมีนัยสำคัญทางสถิติ โดยค่า ABI อาจนำมาใช้ในการพยากรณ์ระดับการสูญเสียความสามารถของร่างกายเบื้องต้นภายหลังเกิดโรคหลอดเลือดสมองตีบหรืออุดตันเฉียบพลันได้*