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# The correlation between C-Reactive Protein, Vascular Cell Adhesion Molecule-1, and S100b with Alberta stroke program early CT Score in non-hemorrhagic stroke patients

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## ABSTRACT

**Background:** Stroke is the leading cause of disability and the second-most cause of death in Indonesia, caused by atherosclerotic obstructions in the cerebral and cervical arteries. C-reactive protein (CRP) is an acute-phase protein synthesized after the stimulation of the pro-inflammatory cytokines. Vascular cell adhesion molecule 1 (VCAM-1) is a sign of both inflammation and atherosclerosis. S100B protein is the dominant protein in the central nervous system released in the event of inflammation in the brain, such as stroke. CT-scan is a gold-standard diagnosis of non-hemorrhagic stroke. However, it has a limit to the onset of <6 hours. The Alberta stroke program early CT-score (ASPECTS) system enhances non-contrast CT-scan sensitivity in assessing early ischemic changes in areas supplied by the middle cerebral artery (MCA). The correlation between inflammatory variables and ischemic assessments on CT-scan needs to be analyzed further. This study aimed to prove the correlation between acute inflammatory signs and ischemic assessment using ASPECTS in non-hemorrhagic stroke patients.
**Methods:** This study was a cross-sectional study conducted in April-September 2019 on 47 non-hemorrhagic stroke patients in Diponegoro National Hospital, Telogorejo Hospital, and Tugurejo Hospital, Semarang. The diagnosis of non-hemorrhagic stroke was based on the non-contrast CT-scan and subsequent ASPECTS assessment. CRP, VCAM-1, and S100B levels were examined using the ELISA principle. The correlation test between variables was also performed employing the Spearman test.
**Results:** The correlation test results between the CRP, VCAM-1, and S100B levels with the ASPECTS were r = -0.035, p = 0.815; r = -0.117, p = 0,432; and r = 0.145, p = 0.332, respectively.
**Conclusions:** There was no significant correlation between the CRP, VCAM-1, and S100B levels with the ASPECTS. The increase in CRP and S100B inflammatory signs was not accompanied by low ASPECTS assessment, which depended on the appearance of lesions on the CT-scan.

**Keywords:** CRP, imaging, score, stroke, VCAM-1, S100B.
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## INTRODUCTION

Stroke is the primary cause of disability and the third leading cause of death (11.8%) worldwide, with a prevalence of non-hemorrhagic stroke of around 80% of all stroke cases.[1,2] In 2013, it was estimated that 25.7 million people worldwide suffered from strokes, and there were 6.5 million deaths worldwide due to stroke. The number of new stroke cases worldwide was 10.3 million per year.[3]

The prevalence of non-hemorrhagic stroke was higher than hemorrhagic stroke both worldwide and in Asian countries.[4] Stroke is a severe problem in Asia, especially in member countries of the Association of South-East Asia Nations (ASEAN). Stroke has been in the top four of the cause of death since 1992, where the first rank was Indonesia, followed by Myanmar, Vietnam, and Thailand, with a prevalence of non-hemorrhagic stroke ranging from 67-93%.[4,5] The Indonesian stroke foundation data stated that stroke was the second leading cause of death in Indonesia among people aged more than 60 years and was the fifth leading cause of death among people aged 15-59 years.[6]

An atherosclerotic obstruction causes Non-hemorrhagic stroke in the cerebral and cervical arteries in the presence of ischemia in all parts of the obstructed artery.[1] Ischemia causes microglia, astrocytes, and endothelium to release cytokines, resulting in leukocyte activation and adhesion to the microvascular

endothelium. These activated leukocytes obstruct the blood vessels, leading to endothelial damage and inflammatory response.[7]

The diagnosis of non-hemorrhagic stroke is based on the disease's history and course, physical, radiological, and laboratory examinations. Objective diagnostic tests can be obtained from the Computerized Tomography (CT)-scan as the gold standard for diagnosing non-hemorrhagic stroke due to its high sensitivity and specificity.[8] However, CT-scan has limitations. In hyperacute non-hemorrhagic stroke (onset of 0-6 hours), it is less sensitive in identifying cerebral infarction.[9] Due to the limitations, radiologists, have agreed to increase the sensitivity in evaluating acute non-hemorrhagic stroke through systematic CT-scan and using the Alberta Stroke Program Early CT Score (ASPECTS) system. The ASPECTS is a systematic and practical method employed as a standard for detecting and reporting the extent of the acute non-hemorrhagic stroke.[10] It is also a scoring system utilized to assess early ischemic change (EIC), which affects the middle cerebral artery (MCA) areas in non-hemorrhagic stroke cases. The areas supplied by the MCA is divided into ten regions in the ASPECTS scoring system.[11,12] Several studies have shown an independent correlation with inflammatory parameters, as well as the size and location of ischemic lesions in the brain.[10,13]

The liver synthesizes CRP as a pro-inflammatory cytokine response with IL-6 as the primary regulator and IL-1 and TNFα to increase CRP transcription. The role of CRP directly helps improve the regulation of VCAM-1 and chemokines in endothelial cells, as well as vascular smooth muscle cells and monocytes. The vital role of VCAM-1 in induced leukocyte migration is a mediator of rolling-type adhesion and firm adhesion, which depends on the avidity status of α4β1 integrin or VLA-4. The ischemic condition of Schwann cells and glial cells causes damage to the blood-brain barrier, leading to the release of S100B into the cerebrospinal fluid and the blood.

Moreover, CRP is an excellent clinical marker due to its stability, high sensitivity, and reliability.[14,15] Hertog et al.[16] stated that non-hemorrhagic stroke stimulates an inflammatory response characterized by the release of acute-phase proteins, such as CRP and cytokines. The inflammatory process starts two hours after stroke onset and lasts several days, contributing to brain damage. The results showed an increase in CRP above the cut-off value was associated with an increased risk of poor outcome and mortality in non-hemorrhagic stroke cases. Ikra et al.[17] and Dewan et al.[18] suggested that the high CRP level is related to the severity and prognosis of non-hemorrhagic stroke.[17,18] The same result was explained by Shah et al.[19] and Neki et al.[19] in their studies.[19,20]

Meanwhile, vascular cell adhesion molecule-1 (VCAM-1) is a biomolecular sign of inflammation and endothelial dysfunction associated with non-hemorrhagic stroke pathophysiology.[21] VCAM-1 can be utilized as a simple marker for atherogenesis, endothelial dysfunction associated with hypertension and atherosclerosis, besides being a diagnostic marker for acute non-acute hemorrhagic stroke. VCAM-1 has a significant correlation with the incidence of angina, myocardial infarction, or extensive atherosclerosis based on angiographic examination.[22-25]

Besides, S100B protein is a protein found both in glial cells and Schwan cells. S100B acts as a stimulator of cell proliferation and migration and an inhibitor of apoptosis and differentiation. Furthermore, S100B has a role in brain development and repair, activation of astrocytes in brain damage, and neurodegenerative processes. Damage to the glial cells causes S100B protein to leak into the extracellular compartment, then into the cerebrospinal fluid and enter the bloodstream. Therefore, S100B can be measured both in cerebrospinal fluid and serum.[26-31]

Beer et al.[32] found that the CRP level and the lesion's extent were related to S100B levels. On the other hand, Yardan et al.[33] stated that the concentration of S100B in healthy people was 50 pg/ml. S100B is widely used as a marker for acute non-hemorrhagic stroke. Increased S100B level is a sign of central nervous system damage and blood-brain barrier leakage. The level was found to increase from 48 to 72 hours after the stroke onset and peak in the first 3 to 4 days.[33] Selcuk et al.[34] affirmed that the S100B level was not influenced by age, sex, comorbid systemic diseases, and the increased S100B level reached the highest value on the third day. The study also found a significant correlation between increased S100B level and infarct volume.[34] Moreover, Sherif et al.[27] uncovered that an increase in S100B level was associated with stroke severity.

The studies mentioned above suggest a significant increase in CRP levels, VCAM-1, and S100B in acute non-hemorrhagic stroke. However, there are limitations of CT-scan in the acute phase, which is the basis of this study. The authors were interested in analyzing the correlation between these three parameters and ASPECTS in patients with non-hemorrhagic stroke. This study's results are expected to be beneficial in the management of patients with acute inflammation conditions.

## METHOD

This study was an observational analytical study with a cross-sectional design, conducted from April to September 2019 in Diponegoro National Hospital, Telogorejo Hospital, and Tugurejo Hospital, Semarang. The study subjects were patients with non-hemorrhagic stroke who were first diagnosed by a neurologist and proven by a non-contrast head CT-scan. Forty-seven patients were admitted to the ER and treated accordingly. A consecutive sampling method was employed for the subjects who met the study's inclusion and exclusion criteria. Data were collected from history taking, physical examination, CT-scan examination, and laboratory examination.

The study variables consisted of the levels of CRP, VCAM-1, S100B, and the ASPECTS. The levels of CRP, VCAM-1, and S100B were measured by the ELISA method. The Infarct area was evaluated utilizing ASPECTS interpreted by a neurologist with a score of 0-10. The data were analyzed using a computer program to perform a normality test and continued with a correlation test between variables, employing the Spearman test. The statistical test results are defined as significant if the p-value is $<0.05$.

## RESULTS

This study was conducted from April to September 2019 in Diponegoro National Hospital, Tugurejo Hospital, and Telogorejo Hospital, Semarang. This study included 96 subjects, but only 47 of them met the inclusion and exclusion criteria. The study data included the subjects' characteristics, as listed in Table 1.

The study subjects' blood pressures were measured, which ranged from normal to elevated. In our study, an increase in blood pressure was seen in most of the subjects. Furthermore, dyslipidemia was also found in some patients, evidenced by the increased total cholesterol, triglyceride, LDL levels, and decreased HDL level. Twelve (25.5%) subjects did not experience dyslipidemia, while the rest did. On the other hand, 23 (48.9%) subjects had diabetes mellitus, evidenced by an increased random blood glucose level (Table 1).

There was an overall increase in the subjects' CRP and S100B levels above the cut-off value. Meanwhile, the VCAM-1 levels in all the subjects were within normal limits. The ASPECTS scoring results showed that most subjects had 7 or above scores, with only 2 (4.3%) subjects having scores of below 7 (Table 1).

The correlation analysis between CRP levels, S100B, and VCAM-1 with the ASPECTS using the Spearman test can be seen in Table 2.

Table 4 shows no significant correlation between the CRP, S100B, and VCAM-1 levels with the ASPECTS, respectively.

**Table 1. The characteristics of the study participant**

| Parameters | Median ± SE | Min – Max Values |
|---|---|---|
| Sex | | |
| Male (number (%)) | 25 (53.2) | |
| Female (number (%)) | 22 (46.8) | |
| Age (years) | 59 ± 1.05 | 39-69 |
| Height (cm) | 158 ± 0.88 | 150-176 |
| Body weight (kg) | 63 ± 1.09 | 45-76 |
| Body Mass Index (kg/m$^2$) | 25.75 ± 0.34 | 18,7-29,6 |
| Systolic blood pressure (mmHg) | 140 ± 3.41 | 100-240 |
| Diastolic blood pressure (mmHg) | 80 ± 1.49 | 60-100 |
| Total cholesterol (mg/dl) | 189 ± 7.40 | 78-374 |
| Triglycerides (mg/dl) | 121 ± 7.46 | 27-358 |
| LDL (mg/dl) | 122 ± 6.15 | 13-204 |
| HDL (mg/dl) | 35 ± 1.99 | 7-69 |
| Urea (mg/dl) | 29,9 ± 2.02 | 11-89 |
| Creatinine (mg/dl) | 0,9 ± 0.005 | 0,55-1,96 |
| Random blood glucose (mg/dl) | 120 ± 13.35 | 67-624 |
| CRP level (mg/L) | 12,55 ± 5.15 | 5-172.66 |
| S100B level (pg/ml) | 1951.8 ± 322.00 | 96-7918.6 |
| V-CAM-1 level (ng/ml) | 224.93 ± 13.41 | 18.63-403.48 |
| ASPECTS | 9 ± 0,2 | 2-10 |

**Table 2. The results of the correlation analysis between the levels of CRP, S100B, and VCAM-1 with the ASPECTS**

| Parameters | ASPECTS | |
|---|---|---|
| | r | p |
| CRP levels | -0.035 | 0.815 |
| S100B levels | 0.155 | 0.297 |
| VCAM-1 levels | -0.117 | 0.432 |

Explanation: * p<0,005 was defined as significant

## DISCUSSION

The study results revealed an increased CRP level in all subjects compared to the normal values (<5). This result is consistent with the previous studies, stating an increased CRP serum level in almost three-quarters of the ischemic stroke patients. This increase indicated an inflammatory response, expansion of tissue injury, or concomitant infection.[16,35,36]

The result of the study exposed that there was an increased S100B level in all subjects. In this case, structural damage, such as ischemia, in Schwann cells and glial cells, will cause damage to the blood-brain barrier, leading to the release of S100B into the cerebrospinal fluid, and the blood. S100B is a reliable marker for the blood-brain barrier permeability. Several studies have found that the S100B level was not influenced by age, sex, systemic disease, and hemolysis samples. Furthermore, the S100B level remained stable for several hours so that no immediate examination was needed. However, the half-life was relatively short, found in the first 48-72 hours, and the peak was in the first 3-4 days.[33,37]

The S100B protein has long been studied as a marker for acute non-hemorrhagic stroke. The S100B also helps differentiate non-vascular vertigo from central vertigo, aiding non-hemorrhagic stroke diagnosis if a head CT scan is not available.[38] Another study confirmed that measuring the S100B levels within 48 to 72 hours after the stroke onset was associated with the degree of neurological deficits and ischemic volume and could predict the patient's prognosis and outcome.[34,39]

The study results showed that the VCAM-1 levels were within normal limits, which differs from the previous studies. Richard et al.[40] conducted a study on 75 non-hemorrhagic stroke patients at 0-6 hours, 6-36 hours, 5-7 days, and 2-3 weeks after the onset. The study concluded that VCAM-1 was an independent predictor at 2–3 weeks after the onset of non-hemorrhagic stroke (OR = 8; 95% CI, 2–37; p = 0.001), with a level of >820 ng/mL (a cut-off value of 820 ng/mg; AUC = 73%). Supanc et al.[41] who carried out a study on 110 acute non-hemorrhagic stroke patients and 93 controls, discovered that the VCAM-1 levels in thromboembolic stroke patients were significantly higher than those in the control groups. However, the study found no significant correlation to the degree of

stroke severity and disability. The normal VCAM-1 level indicated that VCAM-1 was not suitable to be used as a parameter of acute inflammation. Normal VCAM-1 level might be caused by the subjects' consumption of antidyslipidemic or hypertension drugs, causing the inhibition of atherogenesis and no increase in VCAM-1 levels. The normal VCAM-1 level also pointed out that this study's subjects had minimal atherogenesis process.

Further, the study results disclosed no significant correlation between the CRP levels and the ASPECTS. This result is in line with other studies analyzing CRP levels in non-hemorrhagic stroke, although it did not analyze its correlation to the ASPECTS. On the other hand, Topakian et al.[42] revealed that CRP failed as a predictor of outcome in stroke patients receiving intravenous thrombolysis therapy. This result aligns with the study of Winbeck K et al.[43] which also found that CRP level in acute ischemic stroke was not associated with long-term prognosis.[42,43] This study result exhibited that the correlation test between the S100B and VCAM-1 levels with the ASPECTS was not significant. This result is not consistent with the previous studies, which showed that patients with non-hemorrhagic stroke had high S100B and VCAM-1 levels. This result is similar to what has been previously described.

Furthermore, the CRP and S100B levels were not associated with the ASPECTS, although these inflammatory signs' levels were high. Theoretically, they should have a negative correlation, which means that the higher the CRP levels and S100B levels, the lower the ASPECTS will be (below 7). Most subjects had ASPECTS scores of more than 7, which indicated a non-severe extension of the ischemic lesions. Therefore, it could be concluded that despite the high levels of the inflammatory signs, the extent of lesions in non-hemorrhagic patients was not necessarily severe enough to give low ASPECTS scores. This explanation was what made the results insignificant. In this study, the inflammatory signs were measured to assess the patient's inflammatory condition regardless of the ASPECTS scores.

The study also demonstrated no significant correlation between the VCAM-1 levels and the ASPECTS due to the normal VCAM-1 levels. Meanwhile, the ASPECTS was also classified as good, in which most of the scores were 9 and 10. Therefore, VCAM-1 levels could not be used as an inflammatory marker. It showed minimal atherogenesis, which was possibly due to the antidyslipidemic treatments.

This study did not analyze adjusting for comorbid states of non-hemorrhagic stroke that might affect each comorbid state. Future studies need to evaluate other radiological markers associated with inflammatory signs to be investigated thoroughly. A diagnostic study for inflammatory signs of CRP and S100B in non-hemorrhagic patients is also needed.

## CONCLUSION

There was no correlation between the levels of CRP, VCAM-1, and S100B with the ASPECTS. The increased CRP and S100B levels above the normal values could be used as a marker of acute inflammation in non-hemorrhagic stroke patients, which was inconsistent with the extent of the lesion found on the CT-scan.

## CONFLICT OF INTEREST

No conflict of interest.

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## ETHICAL CONSIDERATION

Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine of Universitas Diponegoro with ethical clearance reference number No.45/EC/FK UNDIP/II/2019.

## AUTHOR CONTRIBUTION

All author contributed equally to write the original draft and agreed for final version of the manuscript.

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