# C-Reactive Protein is a Predictor of Early Neurologic Deterioration in Acute Ischemic Stroke

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Although the association between elevated C-reactive protein (CRP) level and long-term outcome after ischemic stroke is well known, the association between CRP and early neurologic deterioration (END) has not yet been thoroughly studied. We investigated the impact of CRP on END in patients with acute ischemic stroke. From a prospectively collected, multicenter stroke registry, 428 patients with acute ischemic stroke diagnosed within 24 hours of onset were enrolled in the study. Patients with hemorrhagic stroke, transient ischemic attack, and thrombolysis were excluded. END was defined as a >2-point increase in the National Institutes of Health Stroke Scale score within a 72-hour period. Data considered potentially associated with CRP level and the END were collected. END was observed in 47 patients. CRP level, time before arrival at the hospital, age, female sex, hematocrit, high-density lipoprotein (HDL) cholesterol level, hemoglobin $A_{1c}$ level, and internal carotid artery occlusion were significantly associated with END. On logistic regression analysis, CRP level, internal carotid artery occlusion, and HDL cholesterol proved to be independent variables. Our data suggest that CRP level at admission is significantly associated with END in acute ischemic stroke. HDL cholesterol and internal carotid artery occlusion are also associated with END. **Key Words:** Brain infarction—neurological manifestation—progression-CRP.


Early neurologic deterioration (END) commonly occurs after the onset of ischemic stroke.[1-5] Many researchers have attempted to identify prognostic factors for END with the aim of mitigating its occurrence. END has been associated with initial stroke severity,[6] classification of stroke,[2,7] presence of large-vessel occlusion,[5,8] extent of infarction,[1] and inflammatory markers.[9] END involves multiple mechanisms, including failure of collateral circulation, clot progression, recurrent stroke, brain edema or herniation, and hemorrhagic transformation.[4] Thus, a single intervention strategy likely would not be effective for all patients. Recently, inflammation has been suggested as a possible mechanism of END.[9] Elevated interleukin (IL)-6 levels and white blood cell counts have been reported in patients with END.[2,9] An effect of elevated levels of the inflammatory marker C-reactive protein (CRP) on cardiovascular or stroke outcome has been reported.[10-14] An elevated CRP level has been reported to predict future stroke events and unfavorable outcome in patients with ischemic stroke.[10,11] The accuracy of admission CRP level in determining END has not yet been sufficiently studied, however. In the present study, we investigated the association between CRP level and END in patients with acute ischemic stroke.

## Subjects and Methods

We retrospectively selected patients who sustained an ischemic stroke between January and December 2008 from a prospectively collected multicenter stroke registry,

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the Korea University Stroke Registry (KUSG). The eligibility criterion for inclusion in the study was acute ischemic stroke with neurologic symptoms in the first 24 hours after stroke onset. For those patients with stroke on awakening, stroke onset was designated as the halfway point between the time when the patient was last symptom-free and when the neurologic deficits became apparent. Ischemic stroke was defined as the presence of focal neurologic deficits explained by the relevant lesions detected on brain magnetic resonance imaging (MRI) or computed tomography scan. An acute lesion found in a subject whose neurologic deficits disappeared within 24 hours of onset was classified as a stroke. Reasons for exclusion from the study included intracranial hemorrhage, intravenous or intra-arterial thrombolysis, incomplete medical records, and early discharge from the hospital (within 3 or fewer days). All participants were treated accordingly, and brain imaging was performed to rule out intracranial hemorrhage and to evaluate cerebral hemodynamic status. If neurologic deterioration occurred during admission, then the attending physician determined whether additional imaging was needed.

Detailed demographic and clinical parameters were recorded. Hypertension was defined as the combination of a self-reported diagnosis of high blood pressure and use of an antihypertensive medication, or blood pressure recordings exceeding 140/90 mm Hg beyond the second week after stroke. Diabetes was defined as a fasting glucose level ≥7.0 mmol/L or self-reported use of insulin or an oral hypoglycemic agent. Levels of total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were analyzed from fasting blood samples obtained within 24 hours of admission. Levels of high-sensitivity CRP, homocysteine, and hemoglobin $A_{1c}$ were assessed as well. Data on smoking status, regular treatment with an antiplatelet or a lipid-lowering agent, and diagnosis of cancer within the previous 5 years were collected. Based on previously published guidelines, the mechanism of stroke was divided into 5 groups,[12] and the topographic pattern of stroke was divided into 4 groups.[13]

The initial volume of infarction (VOI) was measured as described previously.[14] In brief, VOI was calculated by multiplying the infarcted area on each the diffusion-weighted MRI image slice by the section thickness of the image. To express the VOI as a categorical variable, we classified the subjects into one of 4 groups, representing 4 quartiles of VOI.

Serial neurologic assessment was performed using the National Institutes of Health Stroke Scale (NIHSS) scores on admission and at 72 hours after admission. The investigators were trained in applying the NIHSS using a single protocol. END was defined as a >2-point increase in NIHSS score within 72 hours of admission. The causes of END were classified as new lesion, increased lesion size, hemorrhagic transformation, brain edema with or without brain herniation, aggravated medical condition, undetermined cause, and other causes.

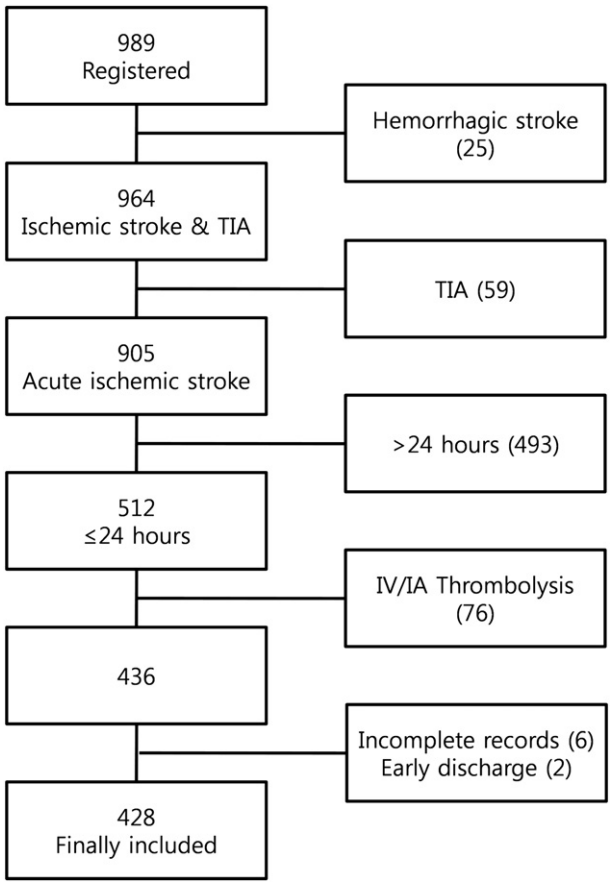


**Figure 1.** *Inclusion and exclusion of subjects.*

All statistical analyses were performed using SPSS version 10.0 (SPSS Inc, Chicago, IL). A $P$ value $<.05$ was considered significant. Differences between groups were evaluated using the independent $t$ test or Mann-Whitney $U$ test. The $\chi^2$ test was used to compare categorical variables,. Logistic regression analysis was performed to investigate possible relationships between the presence of END and other covariates. The results were calculated as adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

## Results

A total of 989 patients were registered at KUSG during the study period (Fig 1). Of these, 561 patients were excluded, due to hemorrhagic stroke (n = 25), transient ischemic attack (TIA; n = 59), hospital arrival more than 24 hours after symptom onset (n = 493), thrombolysis (n = 76), incomplete records (n = 6), and early discharge (n = 2), leaving 428 subjects for analysis (mean age, 66.03 ± 13.76 years; 40.9% female). The mean admission NIHSS score was 5.07 ± 5.27. The mean difference in NIHSS score between admission and 72 hours ($NIHSS_{admission}$ - $NIHSS_{72\ hours}$) was 0.45 ± 2.60. Demographic data,