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# The relationship between oxidized low-density lipoprotein and the NIHSS score among patients with acute ischemic stroke: The SOS-Stroke Study

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ABSTRACT

*Background and aims:* Oxidized low-density lipoprotein (oxLDL) has a defined role in the genesis and development of atherosclerosis, however, whether it is related to severity of neurological deficits is rarely reported. The aim of our study was to investigate the potential association between oxLDL and the National Institutes of Health Stroke Scale (NIHSS) score among patients with acute ischemic stroke.
*Methods:* Between January 2014 and October 2014, we recruited 4111 patients with acute ischemic stroke (AIS), who were admitted within 7 days—43 hospitals in China, and participated in the SOS-Stroke Study. We collected detailed clinical data and then tested the relationship between oxLDL and the NIHSS score using a multivariate linear regression analysis.
*Results:* After adjusting for age, gender, ethnicity, marriage and other confounding variables, the elevated NIHSS score was significantly associated with increased oxLDL levels, and each 1-μg/dL elevation in oxLDL concentration resulted in an increase of 0.027 in the NIHSS score.
*Conclusions:* A positive correlation was found between plasma levels of oxLDL and the NIHSS score in patients with acute ischemic stroke. Higher plasma levels of oxLDL potentially suggest a worse prognosis in AIS patients.



## 1. Introduction

Although data has shown a downward trend of stroke mortality both in urban and rural areas in China in the past 30 years [1], the true burden of stroke has actually increased over the same period [2]. The present situation of stroke is still a main challenge to public health. Ischemic stroke accounts for approximately 80% of all strokes, and one of the leading causes of this type of stroke is atherosclerosis (AS). Oxidized low-density lipoprotein (oxLDL), which is the result of oxidative modification of low-density lipoprotein (LDL), has a defined role in the onset of AS and promotes the whole pathological process. Studies have suggested that oxLDL induces the release of inflammatory cytokines [3], leads to endothelial dysfunction [4] and participates in development of foam cells [5]. In addition, elevated levels of oxLDL have already showed a positive relationship with the severity of acute coronary syndromes and can independently predict endothelial dysfunction in type 2 diabetes [6,7]. Considering the mechanisms underlain may be similar, it seems that plasma levels of oxLDL may be a valuable pathogenic factor for acute ischemic stroke (AIS). Could high levels of oxLDL correlate with the severity of AIS? Since the National

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Institutes of Health Stroke Scale (NIHSS) is a valid and reproducible standard widely used to objectively quantify the impairment caused by AIS [8], we designed a study to assess the relationship between plasma levels of oxLDL and the NIHSS score in patients suffered stroke.

## 2. Patients and methods

### 2.1. Study population

The study cohort was obtained from the Study on Oxidative Stress in Patients with Acute Ischemic Stroke (SOS-Stroke Study), a multi-centre, registered and prospective study. The SOS-Stroke Study was based on a consecutive selected population sample of patients (n = 4164) with AIS. These patients, whose age ranged from 18 to 90 years, had suffered from stroke and were admitted to 43 designated hospitals in China within the previous 7 days. All examinations were performed by specially trained physicians and nurses. The study was sponsored by the Stroke Screening and Prevention Engineering Office of the National Health and Family Planning Commission and was approved by the Ethics Committee of Beijing Tiantan Hospital, Xuanwu Hospital, Capital Medical University and Peking Union Medical College Hospital, and was incompliance with the Declaration of Helsinki. All patients provided informed, written consent.

### 2.2. Inclusion criteria

The inclusion criteria of SOS-Stroke were as follows: (1) patient's age >18 years; (2) diagnosis of AIS made by neurologists and confirmed using computed tomography (CT) or magnetic resonance imaging (MRI); (3) time from initial ischemic attack to diagnosis less than 1 week; (4) patients provided informed, written consent.

### 2.3. Exclusion criteria

The exclusion criteria were as follows: (1) patients with bleeding or other pathological brain diseases (such as vascular malformations), tumours, abscesses, multiple sclerosis, or other common non-ischemic cerebral diseases, as assessed using head CT and/or MRI; (2) individuals with transient ischemic attack; (3) patients with iatrogenic stroke caused by angioplasty or other surgical operations.

### 2.4. Baseline data collection

The 4164 patients enrolled in the study did not receive any antioxidant drugs. Information on patients' demographics and clinical characteristics (age, sex, marital status, alcohol use, education, and history of diseases) was obtained from patients themselves or their relatives according to a questionnaire filled by doctors. Body weight and height were measured and body mass index (BMI) calculated. Blood pressure was measured twice with an appropriate cuff size in relation to arm size, when the patients had been resting in the supine position for 5 min. The average of the two readings was used; however, if the difference between the two measurements exceeded 5 mmHg a third reading was taken, and the average of three readings was used. Heart rate was recorded from electrocardiogram measurements. The main vascular risk factors included history of hypertension (self-reported history of hypertension or use of antihypertensive drugs prior to/during hospitalisation), diabetes mellitus (any self-reported history of diabetes mellitus or use of glucose-lowering drugs prior to/during hospitalisation) and past use of statins (the most recent prescription supply ended within 3 months before admission). NIHSS scores were determined on admission and divided into three grades (mild: NIHSS < 4; moderate: $5 \leq$ NIHSS < 15; severe: NIHSS $\geq$ 15) according to a common consensus of neurological practitioners. Trial of Org 10172 in Acute Stroke Treatment (TOAST) classifications were divided into five types: large-artery atherosclerosis (LAA), cardiac embolism (CE), small-artery lacunar occlusion (SAO), stroke of other demonstrated aetiology (SOE), and stroke of undemonstrated aetiology (SUE).

### 2.5. Biochemical analysis

All biochemical variables except oxLDL were measured using an auto-analyser (Olympus AU400, Japan) at the central laboratories of the 43 designated hospitals in China. Plasma levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were measured using a direct test method (inter-assay coefficient of variation <10%; Mind Bioengineering, Shanghai, China).

### 2.6. Determination of oxLDL levels

OxLDL measurement was performed with plasma samples using an oxLDL ELISA Kit (RapidBio Laboratory, Calabasas, CA, USA) according to the manufacturer's guidelines. Plasma samples were collected from fasting patients on the second day after admission. The samples were centrifuged within the same 24-h period at 2000*g* for 5 min, and the supernatant serum samples were transferred into polypropylene tubes and stored at −80 °C until transportation to Beijing from the 43 designated hospitals. OxLDL levels were measured at the central neurology lab (laboratory of immunology) of Peking University First Hospital.

### 2.7. Statistical analysis

Statistical analysis was performed using SAS software (version 9.3; SAS Institute, Cary, NC, USA). Data were presented as mean ± standard deviation (SD) or median (interquartile range, IQR) for continuous variables and as frequencies and percentages for categorical variables. The ANOVA (analysis of variance) test was used to analyse non-paired samples for the comparison of normally distributed parameters, and the Kruskal–Wallis H test for the comparison of non-parametric variables. The comparison of categorical variables was performed by the chi-squared test. Multivariate linear regression analysis was used for multiple variance analysis. Differences were considered significant only when $p < .05$.

## 3. Results

From a total of 4164 individuals, 53 patients who were not eligible at baseline were excluded from the study, including 27 patients in whom oxLDL could not be detected and 26 for whom the NIHSS scores could not be obtained. Consequently, a total of 4111 patients were enrolled in the present study (mean age, 63.15 ± 12.15 years), 1443 (35.10%) were female and 2668 (64.90%) male. The mean ± SD of the NIHSS scores obtained on admission and the oxLDL levels were 5.72 ± 5.46 and 56.85 ± 20.99 μg/dL, respectively. The median (IQR) oxLDL concentration for the entire group was 62.80 (48.10–70.19) μg/dL.

Table 1 shows the distribution of the baseline characteristics according to different levels of the NIHSS score. Marital status, smoking, and alcohol consumption, and the presence of hypertension, diabetes mellitus, past use of statins, HDL cholesterol, TC, TG and BMI did not differ between the three NIHSS-graded groups. Age ($p < .0001$), gender ($p = .0008$), oxLDL levels ($p < .0001$), LDL