Interleukin-6 as Predictor of One-Year Cognitive Function After Ischemic Stroke or TIA

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Background and Purpose: The relationship between inflammatory markers and cognitive decline in a poststroke setting is still unclear. We aimed to investigate the association between interleukin-6 (IL-6) and cognitive decline after acute ischemic stroke and transient ischemic attack (TIA).

Methods: In this prespecified prospective sub-study of the Impairment of CogniON and Sleep after acute ischemic stroke or transient ischemic attack in Chinese patients (ICONS) study, a total of 1003 patients with baseline IL-6 levels and completed standard 3-month and 1-year cognitive function evaluation were included. Cognitive decline was defined according to a reduction of Montreal Cognitive Assessment (MoCA) ≥2 between 3 months and one year. Multivariable logistic regression analysis was used to determine the association.

Results: Totally, 238 (23.73%) patients had post-stroke cognitive decline at one year. IL-6 levels were classified into four groups according to their quartile. Patients in the highest quartile of IL-6 level had higher risk of cognitive decline than those in the first quartile (25.90% vs 16.80%, adjusted OR, 1.95; 95% CI, 1.13–3.38, P = 0.0167), after adjusting for potential risk factors.

Conclusion: Elevated IL-6 levels were independently associated with reduction of Montreal Cognitive Assessment after ischemic stroke and TIA.

Keywords: inflammation, biomarker, stroke, transient ischemic attack, cognitive decline

Introduction

Stroke is a leading cause of disability worldwide.1 With over 2 million new cases annually, stroke is associated with the highest disability-adjusted life-years loss of any disease in China.2 Up to one-third of stroke patients develop post-stroke cognitive impairment (PSCI).3–5 Strokes affect daily functioning including cognition in addition to executive function, which influenced quality of life and return to work, contributing to a growing health, social and economic burden.6 However, PSCI has been an underestimated complication compared with physical disability. There is an urgent need to early screen and apply intervention treatment for the patients at high-risk of PSCI.

Inflammation has been shown to be a crucial mechanism in cognition impairment.7,8 Interleukin-6 (IL-6) was one of crucial inflammatory biomarkers. Some studies investigated the association between IL-6 and cognitive impairment in the general population; however, the conclusion was controversial.9–15 and limited information was available in stroke patients.16

The ICONS study is a large-scale prospective national registry aiming to investigate the risk factors of cognitive impairment after ischemic stroke or transient ischemic attack (TIA).17 In this subgroup analysis, we investigated the contribution of IL-6 in one-year post-stroke cognitive impairment among patients with ischemic stroke or TIA.
Method

Study Design
Data for this study were obtained from a prespecified prospective substudy of the ICONS study. The ICONS study was a subgroup of China National Stroke Registry-III (CNSR-III), a prospective multicenter registry that enrolled patients within seven days after symptom onset with a diagnosis of acute ischemic stroke or TIA between August 2015 and March 2018 from 201 hospitals that cover 22 provinces and 4 municipalities in China. Of these, 40 sites with experience of cognition, qualified research capability and proved commitment to the study voluntarily participated in the ICONS study. The inclusion and exclusion criteria of the ICONS study have been described before. The inclusion criteria of ICONS were the same as CNSR-III, including: age older than 18 years; in-hospital AIS or TIA patients within 7 days after onset. However, the following exclusion criteria were added to ICONS, including: prior diagnosis of cognitive impairment, schizophrenia or psychosis disease; illiterate patients; and concomitant Neurological disorders that interfere with cognitive or sleep evaluation, for example, severe aphasia defined as National Institutes of Health Stroke Scale (NIHSS) item 9 > 2, visual impairment, hearing loss, dyslexia, severe unilateral neglect or consciousness disorders. Acute ischemic stroke and TIA were defined according to the WHO criteria and confirmed by CT or MRI.

Among the 40 sites in ICONS study, 28 sites voluntarily participated in the biomarker substudy, collected specimens from consecutive patients in these sites. Patients from these 28 sites with baseline IL-6 level and fulfilled 3-month and 1-year cognitive function assessments were included in this study.

This study was conducted in accordance with the Declaration of Helsinki and the protocol of CNSR-III and ICONS was approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2015-001-01) and all participating centers. All patients provided written informed consent.

Baseline Data Collection
Demographics, medical history laboratory data and medication usage during hospitalization were obtained from medical records by unified trained investigators following standard protocol. All the Clinical data were collected through the electronic data capture system (EDC) that automatically checks for integrity and logical corrections of the uploaded data and will improve the data quality.

Inflammatory Markers Assay
Fasting blood samples were withdrawn for all patients within 24 hours of admission. Blood samples were transferred via cold chain to the central laboratory of Beijing Tiantan Hospital and measured blindly. IL-6 concentrations were measured using enzyme-linked immunosorbent assay kits (catalog number: PHS600C, R&D Systems, Inc, Minneapolis, MN, USA).

Cognitive Function Assessment
All participants had Montreal Cognitive Assessment (MoCA) at 3-month and 1-year through face-to-face interviews with a trained research psychologist. Post-stroke cognitive decline was defined as a reduction of MoCA score ≥ 2 between three months and one year.

Statistical Analysis
Continuous variables were given as the median and interquartile range (IQR), whereas categorical variables were represented as frequencies and proportions. Mann–Whitney U-test and the Chi-square test were used for comparison between groups of baseline characteristics. IL-6 level was categorized into four groups according to their quartiles (quartile 1: < 1.59 ng/L, quartile 2: 1.59 to 2.50 ng/L, quartile 3: 2.50 to 4.29 ng/L, quartile 4: ≥4.29 ng/L). We performed crude and multivariate logistic regression models to evaluate the association between IL-6 and post-stroke cognitive decline. The potential confounders were demographic factors, prior published traditional or clinical risk factors and variables associated with outcomes in univariate analysis, with a P-value of < 0.05.
Interactions between IL-6 and age, sex, symptomatic intracranial stenosis, or the Org 10,172 test in the Treatment of Acute Stroke (TOAST) classification and apolipoprotein E (APOE) status on the outcome were further tested by the likelihood ratio tests. In addition, we conducted a mediation analysis to determine whether stroke recurrence could mediate the effect of increased IL-6 level on the risk of cognitive decline after stroke. We used SAS 9.4 software (SAS Institute, Inc, Cary, NC) to conduct the statistical analyses. A two-sided $p$-value of less than 0.05 was considered significant.

Data Availability Statement
All anonymized data in this study could be shared by request from any qualified investigator.

Results
Baseline Characteristics
A total of 1003 consecutive patients were enrolled in this study (Figure 1). The median age was 62 (53–70) years, and 728 (72.58%) patients were males. Among them, 238 (23.73%) patients had post-stroke cognitive decline. Patients in the top quartile of IL-6 levels were older, likely to have history of coronary heart disease and symptomatic intracranial stenosis (Table 1). Compared with patients with no post-stroke cognitive decline, patients with post-stroke cognitive decline were older. There is no difference in other vascular risk factors between two groups (Table 2).

Inflammatory Markers and Post-Stroke Cognitive Performance
The rates of cognitive decline by quartiles of IL-6 were 16.80%, 27.09%, 25.10%, and 25.90%, respectively. In crude models, higher IL-6 level was associated with increased risk of cognitive decline (quartile 2: unadjusted OR 1.84, 95% CI 1.19–2.84; quartile 3: unadjusted OR 1.66, 95% CI 1.07–2.57; quartile 4: unadjusted OR 1.73, 95% CI 1.12–2.68). In the multivariate analysis, after adjusting for age, sex, education level, body mass index, current smoking, heavy drinking, medical history of stroke, transient ischemic attack, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, National Institutes of Health stroke scale score (NIHSS) at admission and symptomatic intracranial artery stenosis, significant association between IL-6 and cognitive decline were observed (quartile 2: OR 1.97, 95% CI 1.22–3.18; quartile 3: OR 1.77, 95% CI 1.09–2.87; quartile 4: OR 1.73, 95% CI 1.05–2.85) (Figure 2). This association remained statistically significant, even further adjusting for one-year stroke recurrence, TOAST classification, white blood cell counts and APOE status (quartile 2: OR 1.94, 95% CI 1.16–3.26; quartile 3: OR 1.73, 95% CI 1.02–2.93; quartile 4: OR 1.95, 95% CI 1.13–3.38) (Figure 2). The risk for the patients in the top quartile of IL-6 increased by 95%
risk for cognitive decline. No significant mediation of stroke recurrence on the association of IL-6 with cognitive decline was found (P > 0.05, Supplementary Table 1).

There was no significant interaction between IL-6 and age, sex, symptomatic intracranial stenosis, TOAST classification or APOE status on the risk of post-stroke cognitive decline (P value for interaction >0.05, Figure 3).

Discussion

In this study, we found that IL-6 was associated with post-stroke cognitive decline at one year in patients with acute ischemic stroke or TIA. Compared to the lowest level of IL-6, the highest level of IL-6 had a 95% increased risk of cognitive decline after stroke.
Several studies have investigated the correlation between IL-6 and cognitive impairment, but the conclusion is controversial.9–14 The Women’s Health and Aging Study II provided evidence that higher IL-6 level was associated with greater declines over 9 years in community-dwelling older women.14 Singh-Manoux et al found that midlife IL-6 predicted cognitive decline, particularly in the reasoning domain.10 In addition, the Prospective Study with Pravastatin in the Elderly at Risk (PROSPER) study demonstrated the IL-6−174 CC genotype was associated with worse cognitive performance, provided the preliminary genetic evidence for the potential causal association.9 However, several studies demonstrated negative association.11,12 In a longitudinal study of older adults from Amsterdam, researchers found declines in processing speed over a 3-year follow-up, but only for high levels of α1-antichymotrypsin, not for high IL-6 levels.11 One of the reasons for this discrepancy might be the difference in study design and populations. On the other hand, much of the prior evidence is based on the general population, the association between IL-6 and cognitive

| Table 2 Baseline Characteristics of Participants According to with or without Post-Stroke Cognitive Decline |
|---------------------------------------------|
| Characteristics                          | PSNCD (n=765) | PSCD (n=238) | P value |
|-------------------------------------------|---------------|--------------|---------|
| Age, year                                 | 61 (53–69)    | 64 (56–71)   | 0.0041  |
| Male                                      | 558 (72.94)   | 170 (71.43)  | 0.6478  |
| Education level                           |               |              | 0.1660  |
| Elementary or below                       | 198 (25.88)   | 51 (21.43)   |         |
| Middle school                             | 262 (34.25)   | 93 (39.08)   |         |
| High school or above                      | 264 (34.51)   | 87 (36.55)   |         |
| Unknown                                   | 41 (5.36)     | 7 (2.94)     |         |
| Body mass index, kg/m²                    | 24.61 (22.77–26.73) | 24.80 (22.86–26.67) | 0.9813 |
| Current smoking                           | 273 (35.69)   | 75 (31.51)   | 0.2375  |
| Heavy drinking                            | 123 (16.08)   | 38 (15.97)   | 0.9672  |
| Medical history                           |               |              |         |
| Stroke                                    | 149 (19.48)   | 60 (25.21)   | 0.0572  |
| TIA                                       | 24 (3.14)     | 9 (3.78)     | 0.6265  |
| Hypertension                              | 483 (63.14)   | 152 (63.87)  | 0.8387  |
| Diabetes mellitus                         | 182 (23.79)   | 58 (24.37)   | 0.8549  |
| Dyslipidemia                              | 91 (11.90)    | 18 (7.56)    | 0.0607  |
| Atrial fibrillation                       | 36 (4.71)     | 14 (5.88)    | 0.4664  |
| Coronary artery disease                   | 90 (11.76)    | 33 (13.87)   | 0.3882  |
| Onset to enrollment time, h               | 15.55 (3.32–44.50) | 10.77 (2.92–31.35) | 0.1477 |
| NIHSS at admission                        | 3.00 (1.00–5.00) | 3.00 (1.00–5.00) | 0.3631 |
| Pre stroke mRS score 2−5                  | 47 (6.14)     | 11 (4.62)    | 0.3797  |
| Index event                               |               |              | 0.1947  |
| TIA                                       | 76 (9.93)     | 17 (7.14)    |         |
| Ischemic stroke                           | 689 (90.07)   | 221 (92.86)  |         |
| Rt-PA treatment                           | 55 (7.19)     | 19 (7.98)    | 0.6825  |
| Symptomatic ICAS                          | 191 (27.44)   | 49 (23.33)   | 0.2369  |
| Medication during hospitalization         |               |              |         |
| Antiplatelet                              | 748 (98.3)    | 234 (98.7)   | 0.6358  |
| Anticoagulants                            | 45 (5.9)      | 8 (3.4)      | 0.1282  |
| Antihypertensive                          | 379 (49.8)    | 124 (52.3)   | 0.4984  |
| Antidiabetic                              | 196 (25.8)    | 68 (28.7)    | 0.3708  |
| Lipid-lowering agent                      | 741 (97.4)    | 231 (97.5)   | 0.9351  |
| Statin                                    | 738 (97.0)    | 229 (96.6)   | 0.9768  |
| White blood cell count, 10⁹/L             | 6.70 (5.59–8.00) | 6.54 (5.70–7.82) | 0.6515 |
| APOE ε4 carriers                          | 113 (17.2)    | 36 (17.0)    | 0.9485  |
| One-year stroke recurrence                | 55 (7.2)      | 24 (10.1)    | 0.1477  |

Note: Variables are presented as median (interquartile range) or number (%).
Abbreviations: mRS, modified Rankin Scale; Rt-PA, recombinant tissue plasminogen activator; APOE, apolipoprotein E; PSCD, post-stroke cognitive decline; PSNCI, post-stroke no cognitive decline; TIA, transient ischemic attack; NIHSS, National Institutes of Health stroke scale; MoCA, Montreal Cognitive Assessment; ICAS, intracranial stenosis.
decline, especially in stroke patients, however, is not yet established.9,16 A prior small sample-sized study found that IL-6 correlated with MMSE scores; however, such relationship disappeared after adjusting for other risk factors.21 Cognitive function was influenced by many elements, such as age, education level, and the state of cerebral blood flow, indicating that discordance of included confounding factors might influence the predictive value of IL-6. Therefore, full adjustment for pertinent predictors is necessary. Previous studies have demonstrated that recurrent stroke during...
follow-up increased the risk of new dementia.\textsuperscript{22} The risk of post-stroke dementia after recurrent stroke is at least 2-fold higher than after the first stroke, more than a third of patients had dementia after recurrent stroke.\textsuperscript{23} We therefore further adjusted stroke recurrence in the current study and explore to what extent, if any, the relationship between IL-6 and cognitive decline was explained by recurrent stroke. However, we did not find any effect from recurrence, suggesting that the association between IL-6 and cognitive decline could not be fully explained by stroke recurrence. In addition, we adjusted for NIHSS scores as they may affect both cognitive function and levels of inflammatory markers.

The pathway IL-6 leading to post-stroke cognition is currently unclear. The chronic inflammatory response after stroke may trigger neurotoxic pathways causing progressive degeneration. Damaged neurons may also exacerbate neuroinflammation-mediated disorders by producing chemokines and activating microglia and astrocytes.\textsuperscript{24} Stroke-induced hypoperfusion can contribute to oxidative stress and endothelial damage, which in turn promote or accelerate neuroinflammation, disruption of the blood-brain barrier, and neurodegeneration.\textsuperscript{25} Another assumption was that systemically produced IL-6 might cross the blood-brain barrier and cause damage in the brain.\textsuperscript{26,27} Experimental evidence supporting this hypothesis derived from the fact that mice overexpressing pro-inflammatory cytokines in the central nervous system exhibit neurodegeneration and cognitive decline.\textsuperscript{28} Taken together, other targeted therapy for prevention of cognitive decline might be needed for the patients with ischemic stroke in addition to existing standard secondary prevention.

In the current study, we used MoCA and evaluated cognitive change between 1-year and three months. Several studies have previously used the Neuropsychological Test Battery and the Mini-Mental State Examination to evaluate cognitive abilities.\textsuperscript{29–32} The major drawback of the long-duration Neuropsychological Test Battery is its lack of feasibility in routine practice or large-scale research. Limitations of the Mini-Mental State Examination are its ceiling effect and lack of assessment of executive defects.\textsuperscript{33} Consequently, MoCA was currently recommended to screen for post-stroke cognitive impairment and is considered the most sensitive screening tool.\textsuperscript{31–36} Furthermore, Wong et al proposed that conventional single cut-off scores were associated with a high rate of misclassification, especially in older and less-educated stroke patients.\textsuperscript{37}

Overall, our results are useful in identifying patients at higher risk of developing post-stroke cognitive decline. The effect of lowering IL-6 levels in preventing or delaying post-stroke cognitive decline and related mechanisms need to be verified in further clinical trials.

Our study had several limitations. First, only one time-point maker measurement is available, which precluded us from assessing the contribution of changes in these markers over time. Second, though MoCA was a useful and practical tool to evaluate cognition, it could not provide information regarding the domain-specific function of cognition. Further investigation with a standardized battery of cognitive tests allowed detailed analyses of cognitive decline were warranted.

**Conclusions**

Elevated IL-6 level was associated with increased risk of reduction of Montreal Cognitive Assessment in patients with ischemic stroke or TIA. This study provides evidence that inflammation may be involved in the underlying mechanism of post-stroke cognitive decline.

**Data Sharing Statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Ethical Statement**

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The CNSR-III was approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2015-001-01) and all participating centers. All patients have provided written informed consent.
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Author Contributions
All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure
The authors report no conflicts of interest in this work.

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