



Relationships of Low Serum Levels of Interleukin-10 With Poststroke Anxiety and Cognitive Impairment in Patients With Clinical Acute Stroke

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Background and Purpose The relationships among interleukin (IL)-10 levels, anxiety, and cognitive status after stroke remain controversial. We aimed to determine the associations of serum IL-10 levels with poststroke anxiety (PSA) and poststroke cognitive impairment (PSCI).

Methods We recruited 350 patients with stroke, of whom only 151 completed a 1-month follow-up assessment. The Mini Mental State Examination (MMSE) and Hamilton Anxiety Scale (HAMA) were used to assess the cognitive status and anxiety, respectively. Serum IL-10 levels were measured within 24 hours of admission.

Results IL-10 levels were significantly lower in the PSA group than in the non-PSA group, and they were negatively associated with HAMA scores ($r=-0.371$, $p<0.001$). After adjusting for all potential confounders, IL-10 levels remained an independent predictor of PSA (odds ratio=0.471, 95% confidence interval=0.237–0.936, $p=0.032$). IL-10 levels were strongly correlated with behavior during interviews, psychic anxiety, and somatic anxiety. Patients without PSCI had higher IL-10 levels than in PSCI patients, and they were positively associated with MMSE scores in the bivariate correlation analysis ($r=0.169$, $p=0.038$), and also with memory capacity, naming ability, and copying capacity. However, IL-10 did not predict PSCI in the univariable or multivariable logistic regression.

Conclusions Low IL-10 levels were associated with increased risks of PSA and PSCI at a 1-month follow-up after stroke. Serum IL-10 levels may therefore be helpful in predicting PSA.

Keywords interleukin-10; stroke; mood disorder; anxiety; cognitive impairment.

INTRODUCTION

Poststroke anxiety (PSA), a type of mood disturbance, is a common psychiatric complication after stroke.¹ PSA is easier to ignore than poststroke depression. Systematic reviews have found that PSA occurs in 20%–30% of stroke survivors.^{2,3} These mood disturbances may negatively affect stroke outcomes and reduce the quality of life.⁴ The prevalence of poststroke cognitive impairment (PSCI) has been reported to range from 10% to 82%. PSCI has been associated with a decreased quality of life, poor functional outcomes, and increased financial burden.^{5–7} Early recognition of PSA and PSCI is therefore important in improving functional outcomes and reducing stroke complication rates. However, the underlying pathophysiological mechanisms of anxiety and PSCI remain unclear.

Ischemic stroke causes a robust local inflammatory response in the brain, which may contribute to secondary brain damage, adverse outcomes, and emotional and cognitive dysfunction.^{8,9} Interleukin (IL)-10 is an anti-inflammatory cytokine associated with several immunomodulatory functions during inflammatory responses.¹⁰ Previous studies have found that IL-10 may exert direct neuroprotective and neurotrophic effects via different

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signaling pathways, including inhibiting proinflammatory cytokine production, reducing antigen-presenting astrocyte or microglia expression, and consequently lowering proinflammatory response levels, reducing endothelial cell damage, and improving vascular dysfunction.^{8,11,12} IL-10 may therefore affect the brain and behaviors through immune regulation, which may impact anxiety, depression, and other affective symptoms.

However, the findings about fluctuating IL-10 levels in mood disorders and cognitive impairments have been inconsistent and often contradictory. Liu et al.¹³ found that increased IL-10 levels may play an anti-inflammatory role in alleviating the inflammatory state of poststroke fatigue. Wiener et al.¹⁴ found that patients with major depressive and bipolar disorders had higher serum IL-6 and IL-10 levels than healthy controls. Several studies also found positive correlations between the serum levels of IL-6 and IL-10 and mood disorders in patients.¹⁴⁻¹⁷ However, a meta-analysis found similar serum IL-10 levels in patients and controls.¹⁸ We previously found that IL-10 levels were higher in patients with poststroke depression.¹⁹ Furthermore, a reduction of IL-10 levels in the amygdala of alcohol-dependent mice was found to be associated with heightened anxiety-like behaviors, including increased alcohol consumption.²⁰ Another study found that subjects with depression had lower IL-10 levels and significantly higher IL-6/IL-10 ratios compared with people without depression.²¹ Meanwhile, there is a growing body of evidence linking IL-10 levels to cognitive function, particularly memory and learning. Specifically, IL-10 may alleviate the harmful effects of inflammatory processes on memory and plasticity by neutralizing the long-term enhancement induced by lipopolysaccharide and IL-1 β release.^{22,23} This neuroprotective effect from IL-10 has been observed in animal models and in patients with Alzheimer's disease (AD).^{24,25} However, other clinical and animal studies found that elevated IL-10 levels may not be beneficial. Abnormal increases in the activity of the IL-10 signaling pathway were observed in some patients with AD.²⁶ Furthermore, in some AD animal models, IL-10 expression was found to accelerate neurodegenerative processes, including increased A β accumulation and memory impairment.^{26,27}

Thus, the associations among IL-10 levels, anxiety symptoms, and cognitive status after stroke remain unclear. This study therefore aimed to determine the relationships among anxiety, cognitive disorders, and IL-10 levels in patients with acute ischemic stroke (AIS).

METHODS

This prospective study was performed at the Department of

Emergency, Neurology and Rehabilitation, and consecutively recruited 350 patients with their first stroke who experienced symptoms within 3 days of being admitted to hospital. The inclusion criteria for patients with stroke were the diagnostic criteria for AIS from the World Health Organization.²⁸ The exclusion criteria were a history of central nervous system disease, such as cognitive impairment, dementia, trauma, hydrocephalus, Parkinson's disease, tumors, or cerebral hemorrhage; a history of a mental or emotional disorder (from clinical diagnosis or previous treatment); severe aphasia or visual or auditory impairment that precluded an assessment; or malignant tumors, severe acute infection, autoimmune diseases, or serious organ dysfunction such as cardiac, liver, or kidney failure. The study protocol was approved by the Medical Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (The Ethics Committee number is issuing number [2018], no. [016]). Written informed consent was obtained from the participants or their next of kin.

Data on the characteristics of the patients were collected within 3 days of admission, including demographic characteristics (age, sex, and years of education), vascular risk factors (smoking, alcohol consumption, hypertension, hyperlipidemia, diabetes, and heart disease), and body mass index (BMI). All patients underwent computed tomography or magnetic resonance imaging (MRI) scans after admission. The cerebral infarction volume of each patient who had undergone MRI should be calculated with the formula $0.5 \times A \times B \times C$, where A is the maximum longitudinal diameter, B is the maximum transverse diameter perpendicular to A, and C is the number of 10-mm sections that contained infarcts. A small cerebral infarction volume was defined as a value of $<5 \text{ cm}^3$.²⁹

Fasting blood samples were collected from patients on the morning after admission at 5–6 a.m. within 24 hours of admission. Serum IL-10 levels were measured using a human cytokine magnetic bead panel kit (HCYT-MAG-60K-PX38, EMD Millipore, Darmstadt, Germany), while other laboratory parameters were tested at the central biochemistry laboratory of the hospital using an automatic biochemical analyzer (Beckman Olympus AU2700, Brea, CA, USA). We divided the patients with cerebral infarction into two groups according to the time that blood was drawn after cerebral infarction onset. One group had blood drawn within 48 hours (short time) and one group within 96 hours (long time) after the onset.

Assessment

Neurologists assessed the stroke severity using the National Institutes of Health Stroke Scale (NIHSS) score within 24 hours

of admission and at discharge, and scores of <7 points were classified as mild stroke.³⁰ The Barthel index (BI) was used to assess the functional outcome of stroke and to evaluate the ability of the patients to live independently.³¹ Cognitive function and anxiety symptoms were assessed by trained neurologists or psychiatrists who were unaware of the clinical manifestations and laboratory test findings of the subjects. They performed these evaluations using the Chinese version of the Mini Mental State Examination (MMSE), Hamilton Depression Scale (HAMD), and Hamilton Anxiety Scale (HAMA) at 1 month after the stroke occurrence. The Chinese versions of the MMSE and HAMA have documented reliability and validity as screening tools for cognitive impairment and anxiety among the Chinese population. Patients with HAMA scores of >7 points were considered to have anxiety, which were determined using the structured clinical interview for diagnostic and statistical manual of mental disorders (DSM-IV).³² Lower MMSE scores indicated more-severe cognitive impairment. Cognition impairment was defined by scores of present illiteracy (≤ 17), primary school education (≤ 20), and secondary school education (≤ 24), respectively.³³

Statistical analysis

All statistical analyses were performed using SPSS Statistics software (version 23.0, IBM Corp., Armonk, NY, USA), and significance was set at $p < 0.05$. Normally distributed, continuous variables were expressed as mean $\pm$ standard-deviation values and were compared using unpaired t -tests. Asymmetrically distributed variables were assessed using the Mann-Whitney U test and expressed as median and interquartile range (IQR) values. Chi-square tests were used to compare proportions. Categorical variables were expressed as frequencies and percentages, and they were compared using chi-square tests. Correlations among HAMA scores, MMSE scores, IL-10 levels, and each variable were analyzed using the Spearman correlation coefficient. Univariable logistic regression accounted for potential confounders and examined potential risk factors for PSA and PSCI. We considered factors with $p < 0.2$ in the univariable regression to be possible confounders. Logistic regression results were presented as adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Receiver operating characteristic curves were used to assess the accuracy of IL-10 levels in predicting PSA and PSCI, with the model accuracy assessed using the area under the curve (AUC).

RESULTS

Baseline characteristics

We recruited 350 patients to participate in this study. The inclusion criteria was met by 198 patients, and 151 patients (mean age=62.81 years; 58.9% males) completed follow-up assessments at 1 month after the onset of stroke. At the time of follow-up assessments, 60 patients presented anxiety symptoms and 77 presented cognitive dysfunction; the incidence rates of PSA and PSCI were 39.7% and 51.0%, respectively. Among the patients whose blood was drawn within 48 hours of admission, 41 (68.3%) had PSA and 56 (61.5%) did not. Among those whose blood was drawn within 96 hours of admission, 46 (59.7%) developed PSCI and 51 (68.9%) did not. We found that the time that blood was drawn did not differ significantly between patients with and without PSA or those with and without PSCI who presented to the hospital within 3 days of onset.

The characteristics of the patients are listed in Table 1. The age, sex, BMI, years of education, systolic and diastolic blood pressures at admission, hospital stay, hospital expenses, and vascular risk factors (e.g., hypertension, hyperlipidemia, diabetes, cardiac diseases, smoking, and alcohol consumption) did not differ significantly between patients in the PSA and non-PSA groups. However, patients with PSCI were more likely to be older and less educated ($p < 0.05$). Those with PSA and PSCI also had more-severe stroke, larger cerebral infarction volume, more-severe depressive symptoms, and worse scores for the activities of daily living ($p < 0.05$) (Table 1). Moreover, the cognitive function was worse in the PSA group (MMSE score IQR: 20.00, 14.25–24.00) than in the non-PSA group (MMSE score IQR: 22.00, 17.00–25.00, $p = 0.045$), while the anxiety symptoms were worse in the PSCI group (HAMA score IQR: 6.00, 3.00–9.00) than in the non-PSCI group (HAMA score IQR: 3.00, 1.00–7.25, $p = 0.008$). HAMA scores were negatively associated with MMSE scores in the bivariate correlation analysis ($r = -0.173$, $p = 0.034$).

Relationship between serum IL-10 levels and PSA

In this study, IL-10 levels were markedly lower in patients with PSA (median=0.60 pg/mL, IQR=0.44–0.94 pg/mL) than in those without PSA (median=1.17 pg/mL, IQR=0.69–2.66 pg/mL, $p < 0.001$) (Fig. 1). Serum IL-10 levels were negatively associated with HAMA scores in the bivariate correlation analysis ($r = -0.371$, $p < 0.001$). Significant associations were also found between HAMA scores and infarction volume, NIHSS score, and BI ($p < 0.05$) (Table 2). Weak positive correlations were also found between HAMA scores and the hospital stay (days, $r = 0.169$, $p = 0.038$) and expenses ($r = 0.151$, $p = 0.064$). IL-10 levels were closely related to behavior dur-

Table 1. Clinical and demographic characteristics of patients with acute ischemic stroke

Characteristic	Groups based on HAMA scores (n=151)		p	Groups based on MMSE scores (n=151)		p
	PSA (n=60)	Non-PSA (n=91)		PSCI (n=77)	Non-PSCI (n=74)	
Demographic parameters						
Age (yrs)	62.43±10.14	63.05±9.78	0.707	64.78±9.65	60.76±9.80	0.012
Sex (male)	32 (53.3)	57 (62.6)	0.257	45 (58.4)	44 (59.5)	0.899
Weight (kg)	63.23±10.18	63.58±10.62	0.845	61.95±10.78	64.99±9.85	0.073
Height (cm)	162.68±8.17	163.54±7.05	0.495	162.51±7.34	163.92±7.66	0.249
BMI (kg/m²)	23.82±2.90	23.72±3.38	0.840	23.40±3.39	24.14±2.94	0.155
Education (yrs)	3.00 (0.00–6.00)	3.00 (0.00–6.00)	0.284	3.00 (0.00–6.00)	5.00 (0.75–8.00)	0.025
Vascular risk factors						
Hypertension	52 (86.7)	76 (83.5)	0.599	67 (87.0)	61 (82.4)	0.435
Hyperlipidemia	23 (20.0)	15 (16.4)	0.582	12 (16.6)	15 (20.3)	0.454
Diabetes	19 (38.3)	26 (28.6)	0.211	25 (32.4)	24 (32.4)	0.996
Cardiac disease	7 (11.7)	11 (12.1)	0.938	7 (9.1)	11 (14.9)	0.275
Smoking	18 (30.0)	29 (31.9)	0.809	24 (32.6)	23 (31.1)	0.991
Alcohol drinking	14 (23.3)	25 (27.5)	0.571	20 (26.0)	19 (25.7)	0.967
SBP at admission (mm Hg)	163.50±26.42	161.41±23.34	0.610	164.36±25.37	160.03±23.62	0.279
DBP at admission (mm Hg)	86.37±15.22	84.90±13.08	0.529	85.52±14.88	85.45±12.98	0.974
Lesion location			0.764			0.958
Cerebral lobes	3 (5.0)	8 (8.8)		5 (6.5)	7 (9.5)	
Basal ganglia and thalamus	34 (56.7)	41 (45.1)		41 (53.2)	34 (45.9)	
Brainstem and cerebellum	10 (16.7)	24 (26.4)		12 (15.6)	22 (29.7)	
Multiple infarction	13 (21.7)	18 (19.8)		19 (24.7)	12 (16.2)	
Stroke etiological subtypes			0.198			0.005
Large-artery atherosclerosis	44 (73.3)	56 (61.5)		60 (77.9)	40 (54.1)	
Cardioembolic	3 (5.0)	10 (11.0)		3 (3.9)	10 (14.1)	
Small-vessel disease	12 (20.0)	25 (27.5)		13 (16.9)	25 (33.8)	
Other or unknown cause	1 (1.7)	0 (0)		1 (1.3)	0 (0)	
Time from onset to blood drawing			0.396			0.241
Short time, <48 hours	41 (68.3)	56 (61.5)		46 (59.7)	51 (68.9)	
Long time, <96 hours	19 (31.7)	35 (38.5)		31 (40.3)	23 (31.1)	
Clinical characteristics						
NIHSS score at admission	4.00 [3.00–7.00]	3.00 [2.00–4.00]	0.001	4.00 [2.00–6.00]	3.00 [2.00–4.00]	0.030
NIHSS score at discharge	4.00 [2.00–6.00]	3.00 [1.00–4.00]	0.001	4.00 [2.00–6.00]	3.00 [1.00–4.00]	0.040
Infarction volume (cm³)	1.92 [0.72–4.98]	0.93 [0.38–2.08]	0.006	1.83 [0.84–4.89]	0.78 [0.24–1.87]	<0.001
SBI	48 (80.0)	78 (85.7)	0.948	65 (84.4)	61 (64.9)	0.900
WMH	41 (68.3)	70 (76.9)	0.570	59 (76.6)	52 (70.2)	0.439
Hospital stay (days)	9.00 [8.00–13.75]	9.00 [7.00–11.00]	0.096	9.00 [7.50–12.00]	8.00 [7.00–11.00]	0.193
Hospital expenses (CNY)	12,044 [10,212–16,482]	11,596 [9,450–14,729]	0.284	11,946 [10,229–14,849]	11,450 [9,348–15,841]	0.434
BI at discharge	90.00 [80.00–100.00]	100.00 [93.75–100.00]	0.002	95.00 [85.00–100.00]	100.00 [90.00–100.00]	0.045
HAMD score	8.50 [6.25–11.00]	2.00 [0.00–5.00]	<0.001	6.00 [3.00–9.00]	3.00 [1.00–7.00]	0.004
Laboratory tests						
Neutrophils (×10 ⁹ /L)	3.80 [3.02–4.76]	3.88 [2.97–5.07]	0.876	3.76 [2.96–4.28]	4.18 [3.14–5.25]	0.042
Lymphocytes (×10 ⁹ /L)	1.97±0.60	1.90±0.60	0.499	1.85±0.59	2.01±0.61	0.114
Erythrocyte count (×10 ¹² /L)	4.57±0.47	4.47±0.54	0.242	4.46±0.45	4.57±0.57	0.173
Hemoglobin (g/L)	136.28±18.83	136.49±17.23	0.943	135.22±17.17	137.65±18.50	0.404
hs-CRP (mmol/L)	2.49 [1.12–3.71]	1.61 [0.65–4.22]	0.271	2.03 [0.93–3.67]	1.67 [0.67–4.25]	0.803
Platelet count (10 ⁹ /L)	230.80±64.72	209.41±55.45	0.046	217.57±63.74	218.26±56.32	0.944
IL-10 (pg/mL)	0.60 [0.44–0.94]	1.17 [0.69–2.66]	<0.001	0.70 [0.50–1.45]	1.07 [0.65–2.14]	0.006

Data are mean±standard deviation, n (%), median (range), or median [interquartile range] values.

BI, Barthel index; BMI, body mass index; DBP, diastolic blood pressure; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; MMSE, Mini Mental State Examination; NIHSS, National Institutes of Health Stroke Scale; PSA, poststroke anxiety; PSCI, poststroke cognitive impairment; SBI, silent brain infarction; SBP, systolic blood pressure; WMH, white-matter hyperintensity.

ing interviews, anxiety symptoms (e.g., anxious mood, tension, fear, insomnia, and depressed mood; $p<0.05$), and somatic anxiety (e.g., muscular system and autonomic symptoms, $p<0.05$) (Table 3).

IL-10 levels were associated with PSA in the univariable logistic regression analysis (OR=0.409, 95% CI=0.254–0.659, $p<0.001$). After adjusting for all potential confounders ($p<0.2$

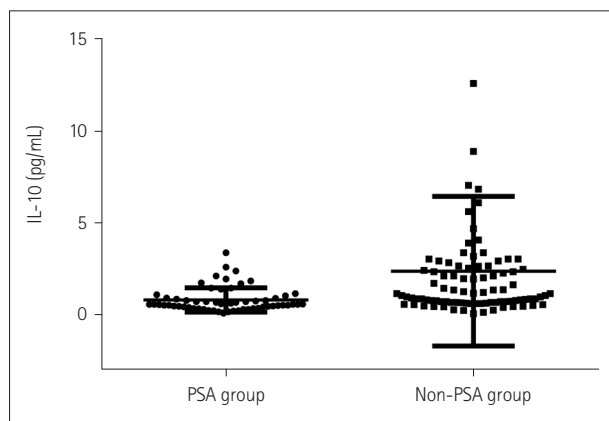


Fig. 1. IL-10 levels in patients with and without PSA. IL, interleukin; PSA, poststroke anxiety.

Table 2. Correlation coefficients for the relationships between HAMA and MMSE scores and other variables

	<i>r</i>	<i>p</i>
HAMA score		
Infarction volume	0.262	0.002
NIHSS score at admission	0.384	<0.001
NIHSS score at discharge	0.419	<0.001
Hospital stay	0.169	0.038
Hospital expenses	0.151	0.064
BI at discharge	-0.367	<0.001
HAMD score	0.860	<0.001
MMSE score	-0.173	0.034
IL-10	-0.371	<0.001
MMSE score		
Age	-0.292	<0.001
Height	0.183	0.025
Weight	0.153	0.061
Hospital stay	-0.184	0.024
BI at discharge	0.145	0.078
Infarction volume	-0.257	0.002
NIHSS score at admission	-0.181	0.026
HAMD score	-0.248	0.002
HAMA score	-0.173	0.034
Erythrocyte count	0.166	0.041
IL-10	0.169	0.038

BI, Barthel index; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; IL, interleukin; MMSE, Mini Mental State Examination; NIHSS, National Institutes of Health Stroke Scale.

in the univariable regression), the significant independent association between IL-10 and PSA remained (Model 1: OR=0.471, 95% CI=0.237–0.936, $p=0.032$; Model 2: OR=0.473, 95% CI=0.261–0.960, $p=0.031$; Model 3: OR=0.500, 95% CI=0.261–0.960, $p=0.037$; Model 4: OR=0.494, 95% CI=0.246–0.989, $p=0.047$; Model 5: OR=0.485, 95% CI=0.236–0.993, $p=0.048$; the four models are defined in Table 4). The AUC value of PSA for predicting functional outcomes was 0.737 (95% CI=0.658–0.817, $p<0.001$) with sensitivity and specificity values of 83.5% and 55.5%, respectively, when the cutoff value for IL-10 level was 0.385 pg/mL (Fig. 2). The

Table 3. Correlation coefficients for the relationships between IL-10 levels and HAMA scores

IL-10 level	<i>r</i>	<i>p</i>
Psychic anxiety		
Anxious mood	-0.335	<0.001
Tension	-0.374	<0.001
Fears	-0.365	<0.001
Insomnia	-0.177	0.030
Cognitive	-0.053	0.515
Depressed mood	-0.388	<0.001
Somatic anxiety		
Muscular system	-0.199	0.014
Sensory system	-0.071	0.386
Cardiovascular symptoms	-0.074	0.368
Respiratory symptoms	-0.137	0.094
Gastrointestinal symptoms	-0.054	0.506
Genitourinary symptoms	-0.120	0.143
Autonomic symptoms	-0.176	0.030
Behavior during interviews	-0.306	<0.001
HAMA score	-0.371	<0.001

HAMA, Hamilton Anxiety Scale; IL, interleukin

Table 4. Findings for a logistic regression model with predictors of poststroke anxiety

Adjusted model type	IL-10 level (pg/mL)	<i>p</i>
Model 1	0.471 (0.237–0.936)	0.032
Model 2	0.473 (0.239–0.934)	0.031
Model 3	0.500 (0.261–0.960)	0.037
Model 4	0.494 (0.246–0.989)	0.047
Model 5	0.485 (0.236–0.993)	0.048

Data are odds ratio (confidence interval) values. Model 1: adjusted for confounding factors with $p<0.2$ (including hospital stay, BI at discharge, Hamilton Depression Scale score, MMSE score, platelet count, IL-10 level, and NIHSS scores at admission and discharge). Model 2: adjusted for confounding factors with $p<0.05$ (Model 1 excluding MMSE score). Model 3: adjusted for the confounding factors in Model 1 excluding NIHSS score and BI at discharge. Model 4: adjusted for the confounding factors in Model 2 and age, sex, and infarction volume. Model 5: adjusted for the confounding factors in Model 3 and age, sex, and infarction volume.

BI, Barthel index; IL, interleukin; MMSE, Mini Mental State Examination; NIHSS, National Institutes of Health Stroke Scale.

combination of IL-10 levels and HAMD scores also had greater accuracy than the IL-10 levels alone in predicting PSA (AUC=0.939, 95% CI=0.903–0.975, $p<0.001$).

Relationship between serum IL-10 levels and PSCI

IL-10 levels were higher in patients without PSCI (median=1.07 pg/mL, IQR=0.65–2.14 pg/mL) than in those with PSCI (median=0.70 pg/mL, IQR=0.50–1.45 pg/mL, $p=0.006$) (Fig. 3). Serum IL-10 levels were positively associated with MMSE scores in the bivariate correlation analysis ($r=0.169$, $p=0.038$) (Table 2). IL-10 levels were positively correlated with registration ($r=0.321$, $p<0.001$), naming ($r=0.286$, $p<0.001$), and copying ($r=0.210$, $p=0.010$) abilities. Moreover, MMSE scores were correlated with age ($r=-0.292$, $p<0.001$),

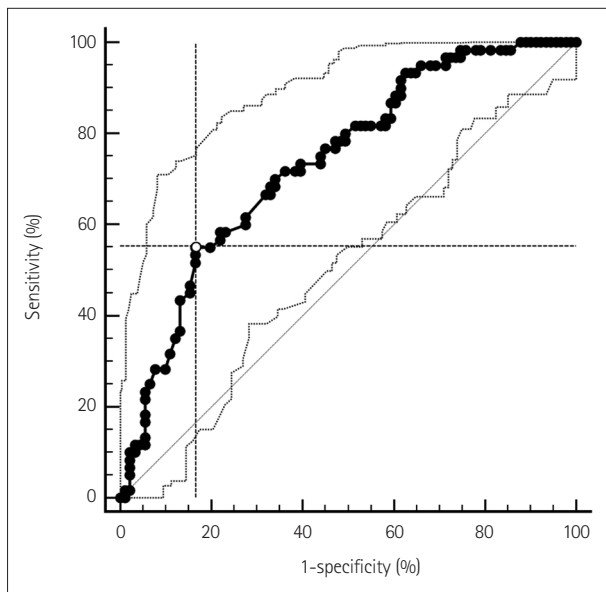


Fig. 2. Receiver operating characteristic curve of interleukin-10 for predicting PSA. The point indicates the optimal cutoff value for predicting PSA, and dashed lines are 95% confidence intervals. PSA, poststroke anxiety.

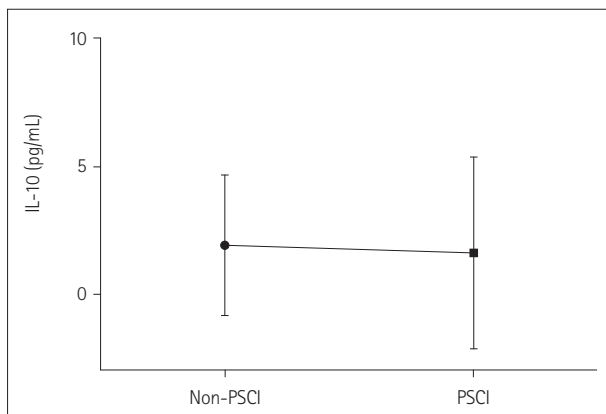


Fig. 3. IL-10 levels in patients with and without PSCI. IL, interleukin; PSCI, poststroke cognitive impairment.

and with the hospital stay, infarction volume, NIHSS score at admission, and HAMD and HAMA scores ($p<0.05$) (Table 2). Furthermore, MMSE scores were correlated with the erythrocyte count ($r=0.166$, $p=0.041$).

However, IL-10 levels had no predictive effect on PSCI in the univariable or multivariable logistic regression analyses (unadjusted OR=0.970, 95% CI=0.875–1.076, $p=0.564$).

DISCUSSION

The findings of this study suggest that serum IL-10 protects emotional and cognitive function after a cerebral infarction. We found a significant correlation between IL-10 levels and HAMA and MMSE scores, and observed that IL-10 levels were lower in patients with PSA. IL-10 levels were strongly correlated with behavior during interviews, psychic anxiety, and somatic anxiety. After adjusting for potential confounders, the IL-10 level was an independent predictor of PSA. IL-10 levels were also significantly lower in patients with PSCI, and they were positively correlated with memory capacity, naming ability, and coping capacity. However, IL-10 levels had no predictive effect on cognitive dysfunction after stroke.

This was the first study that we were aware of to investigate the relationship between IL-10 levels and PSA and PSCI in patients with acute cerebral infarction. Previous studies have found a relationship between serum IL-10 levels and mood disorders, although this association was not consistent in all studies. Dhabhar et al.²¹ found that subjects with depression had significantly lower IL-10 levels, and participants with higher self-rated scores on the inventory for depressive symptomatology had lower IL-10 levels. This result was consistent with our previous study finding that low IL-10 levels were more likely to present in poststroke depression.¹⁹ Meanwhile, a previous cross-sectional study found that mood disorders were associated with IL-6 and IL-10 levels that were higher than those observed in healthy controls.¹⁴ Another study found elevation of IL-6 and IL-10 levels in patients with major depressive disorder.³⁴ Moreover, Patel et al.²⁰ found that local changes in IL-10 levels in the brain may directly impact behavior, and the overexpression of IL-10 in the amygdala was sufficient to suppress anxiety-like behaviors in mice. Animal research has also found that 3-deoxyadenosine levels may upregulate anti-inflammatory factors (e.g., IL-10) and downregulate proinflammatory factors in macrophages and mononuclear cells to play an antianxiety role,³⁵ suggesting that increased serum IL-10 levels reduce anxiety symptoms; this finding was consistent with that of the present study. Serum IL-10 levels may therefore protect against emotional disorders in patients with cerebral infarction.

There is increasing evidence of an association between

IL-10 levels and cognitive function, but findings have been inconsistent. Kulesh et al.³⁶ found that serum levels of IL-10 and other inflammatory factors were associated with memory function and the clinical, neuropsychological, and functional characteristics of patients with AIS. In contrast, Patarella et al.³⁷ did not observe any significant correlation between IL-10 levels and cognitive performance in patients with multiple sclerosis. Similarly, another study found that inflammatory markers might not be useful in ascertaining the risks of cognitive decline and mild cognitive impairment in the general population.³⁸ Some studies have suggested that IL-10 levels alone do not effect cognitive function; meanwhile, one study found a significant interactive effect of IL-10 levels on catechol-o-methyltransferase polymorphisms in several cognitive functions.³⁹ Xiu et al.⁹ also found that lower serum IL-10 levels were associated with reduced attention in patients with genetic variants of schizophrenia, suggesting that the IL-10 gene and its receptors in the healthy human brain regulate inflammation and synaptic function that are important for cognition; its deficiency in schizophrenia may consequently contribute to cognitive impairment. IL-10-related anti-inflammatory pathways may play important roles in preventing or ameliorating cognitive dysfunction. A neuroprotective effect from IL-10 has been observed in animal models and in patients with AD.^{24,25}

Our study found that serum IL-10 levels was significantly lower in patients with cognitive impairment. IL-10 levels were positively correlated with registration, naming, and copying abilities. These findings suggest that serum IL-10 helps to protect against cognitive deficits after stroke. However, other studies found that increased serum IL-10 levels were not always advantageous; in fact, the activity of the IL-10 signaling pathway is abnormally increased in the brains of some patients with AD.²⁶ An animal study demonstrated that IL-10 expression has a proamyloidogenic effect in an amyloid precursor protein mouse model, which leads to dysregulation of immune protein homeostasis, impaired memory, and reduced synaptic marker expression.²⁷ Another animal study found that IL-10 deficiency may help salvage synaptic toxicity and mitigate behavioral disorders in mice with amyloid precursor protein, and “rebalances” innate immunity by blocking the anti-inflammatory response of IL-10, which may be relevant to AD therapy.⁴⁰ Overall, these findings suggest that IL-10 affects the innate immunity, proteostasis, and neurodegenerative processes of the brain, indicating that it a key factor in brain development and function.²⁷

In addition, Munshi et al.⁴¹ found that treatment with peripheral anti-inflammatory cytokine IL-10 may mitigate IL-1 β -induced anxiety and pathological behaviors in adult male rats. Studies of IL-10-knockout mice found that depressive

symptoms detected using several behavioral tests were reversed by an IL-10 injection.^{42,43} These findings highlight the potential of IL-10 for treating mood disorders after stroke.

The present study had some limitations that should be considered when interpreting its findings. First, serum IL-10 levels were only measured once, and the fluctuation of IL-10 levels at different stages of AIS requires further investigation. Second, this was a single-center study with a small sample, which puts it at risk of selection bias. Future large multicenter randomized controlled trials are required to reduce the effects of random variation. Third, many patients could not come to the hospital to complete the follow-up assessments due to long journeys and various other inconveniences, which resulted in a high rate of no follow-up data. Because they did not complete these assessments, we could not perform emotional and cognitive analyses of these patients. However, we still followed up on this aspect of the patients by communicating on the telephone and completed the follow-up to obtain information on the cerebral infarction prognosis and life satisfaction. Fourth, we took 2–3 days to record the cases that come to the hospital more than 24 hours after disease onset. The exact time was not accurate, which prevented an analysis of the exact time between onset and blood drawing, as they could only be divided into “short time” and “long time” groups.

In conclusion, this study found that patients with low IL-10 levels were more likely than those with high levels to develop PSA and PSCI at 1 month after stroke. IL-10 levels were strongly correlated with behavior during interviews, psychic anxiety, and somatic anxiety. After adjusting for potential confounders, serum IL-10 levels emerged as an independent protective predictor for PSA. IL-10 levels were also positively correlated with memory capacity, naming ability, and coping capacity. An increasing number of studies have confirmed the potential of IL-10 in treating mood disorders, and so IL-10 may become a promising biomarker for predicting and treating PSA and PSCI in the future.

Availability of Data and Material

The data sets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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