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Predictive Value of Combined Serological Indicators for Cognitive Dysfunction in Patients with Systemic Lupus Erythematosus

Guimin Zheng[1], Lei Wang[2], Jingjing Cao[1], and Xiao Zheng[3]

[1] Department of General Medicine, Hebei General Hospital, Shijiazhuang, Hebei Province, China
[2] Department of Medical Imaging, Hebei General Hospital, Shijiazhuang, Hebei Province, China
[3] Department of Rheumatology, Hebei General Hospital, Shijiazhuang, Hebei Province, China

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ABSTRACT

Cognitive dysfunction (CD) is a common neuropsychiatric manifestation of systemic lupus erythematosus (SLE), but its early identification lacks objective serological markers. This study aimed to explore the predictive value of combined serum interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), and neurofilament light chain (NfL) for CD in SLE patients.

A total of 108 SLE patients (January 2018–December 2019) and 50 healthy controls were enrolled. SLE patients were divided into CD group (MoCA score<26, n=49) and non-CD group (MoCA score ≥26, n=59). Serum IL-6, ICAM-1, and NfL levels were detected by ELISA. Logistic regression and ROC curve analyses were performed to evaluate risk factors and predictive efficacy.

Serum IL-6, ICAM-1, and NfL levels were significantly higher in SLE patients than in controls, and further elevated in the CD group. These three markers were independent risk factors for SLE-related CD. The AUC of combined detection (0.852) was significantly higher than individual markers (0.734, 0.712, 0.677).

Serum IL-6, ICAM-1, and NfL have certain predictive value for CD in SLE patients, and the combined detection of these three indicators offers higher predictive value.

Keywords: Cognitive dysfunction; Intercellular adhesion molecule-1; Interleukin-6; Neurofilament light chain; Systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that affects multiple systems, and is influenced by genetic, environmental, and immune factors. SLE patients commonly present with clinical symptoms involving the skin, heart, kidneys, lungs, and hematological system, along with significant neuropsychiatric manifestations.[1] When SLE involves the neuropsychiatric system, it is termed neuropsychiatric systemic lupus erythematosus (NPSLE), with cognitive dysfunction being a major manifestation. However, cognitive dysfunction in SLE patients is often under-recognized by clinicians, leading to a low diagnostic rate, persistent symptoms, and impaired quality of life.[2,3] With improved medical standards, SLE treatment has become more standardized, reducing mortality and increasing long-

Corresponding Author: Guimin Zheng, MD;
Department of General Medicine, Hebei General Hospital, Shijiazhuang, Hebei Province, China. Tel: (+86 130) 9109 3566, Fax: (+86 311) 8222 0422, Email: z_gm90030182@hotmail.com

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term survival. The harm caused by cognitive dysfunction has become increasingly prominent,[4] and the particularity of SLE with cognitive impairment poses significant challenges for early diagnosis and intervention. Therefore, early identification and intervention of cognitive dysfunction in SLE patients are of great significance for improving patient outcomes.

Currently, the diagnosis of cognitive dysfunction in SLE mainly relies on neuropsychological assessment tools, with the Montreal Cognitive Assessment (MoCA) scale widely used due to its sensitivity and specificity for screening mild cognitive impairment.[4-6] In addition, with the ongoing progress of medical research, serum markers, as important indicators reflecting the physiological and pathological states of the body, are playing an increasingly important role in the diagnosis and prognostic assessment of various diseases. Serum testing, with its minimal invasiveness and high reproducibility, is widely used for the auxiliary diagnosis of various diseases. Neurofilament light chain (NfL) is a structural scaffold protein specifically expressed in central and peripheral neurons. It is released into the peripheral bloodstream via cerebrospinal fluid during neurodegenerative diseases, inflammation, or trauma. Studies have found that serum NfL levels are considered markers of neuronal injury.[7] Interleukin-6 (IL-6) is a pro-inflammatory cytokine that plays an important role in immune regulation and inflammatory responses in the body and is involved in the pathogenesis of various autoimmune diseases. Studies have shown that IL-6 can mediate B-cell differentiation, promote the expression of autoantibodies, and regulate the proliferation of T-cells, thereby participating in the pathogenesis of SLE. It may also contribute to cognitive dysfunction by stimulating the nervous system and affecting neurotransmitter secretion.[8-10] Additionally, previous studies have shown that the expression of various inflammatory factors, including IL-6, is upregulated in the serum of SLE patients, which has auxiliary diagnostic value for SLE.[11] Intercellular adhesion molecule-1 (ICAM-1) is a transmembrane protein and a member of the immunoglobulin superfamily. It enhances the adhesion between immune cells by binding to specific receptors, playing an important role in immune and inflammatory responses in the body. Studies have shown that ICAM-1 regulates the production of immunoglobulins in SLE, enhances B-cell adhesion to induce pathological antibody production, and is involved in the development of SLE.[12,13] Although previous studies have explored the association of IL-6, ICAM-1, and NfL with cognitive dysfunction separately, the synergistic effect and combined diagnostic value of these three markers in SLE patients with cognitive dysfunction remain unclear. Therefore, this study used the MoCA scale to assess cognitive dysfunction in SLE patients and analyzed the impact factors of cognitive dysfunction in SLE and the diagnostic utility of serum levels of IL-6, ICAM-1, and NfL for cognitive dysfunction in SLE, providing a basis for clinical assessment and intervention of cognitive dysfunction in SLE patients.

METHODS

Research Object

We enrolled a cohort of 108 SLE patients who received treatment at our hospital between January 2018 and December 2019. Inclusion criteria were as follows: (1) Every patient satisfied the 2009 American College of Rheumatology diagnostic criteria for SLE[14]; (2) patients with complete clinical records; and (3) participants aged 18 years or older. Exclusion criteria were as follows: (1) patients with neurological symptoms caused by infections, electrolyte disturbances, uremia, metabolic disorders, drugs, or other factors; (2) patients with acute exacerbation of neuropsychiatric lupus or other acute complications; (3) patients with severe visual or hearing impairments that could affect the examination; (4) patients with a history of severe head trauma, stroke, cerebral hemorrhage, mental illness, or long-term use of antipsychotic drugs or drugs that could affect cognitive function; (5) patients with other diseases that could affect cognition; and (6) patients with a history of alcohol abuse or a family history of mental illness. Additionally, the Medical Ethics Committee of Hebei General Hospital examined this study. This study was approved by the Ethics Committee of Hebei General Hospital.

Research Methods

Data Collection

Based on the sample size calculation formula, we calculated the required sample size. Considering the research objectives and comprehensively referring to relevant data from similar studies, the expected sensitivity is set at 90%, the specificity at 85%, and the allowable error at 10%. The calculation indicated, each group would require at least 42 patients. Therefore, the

total sample size should be at least 84 cases. Taking into account a 10% dropout rate and actual conditions, 108 SLE patients were finally included, which meets the study's power requirement.

All enrolled SLE patients had their general and clinical data collected. General data included gender, age, and education level. Clinical information encompassed disease duration, prior medical history, and family medical background. The SLE Disease Activity Index (SLE-DAI) was assessed using the SLEDAI 2000 scoring system, and cumulative organ damage was evaluated using the Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI). The SLICC-DI covers 12 organ systems, including the kidneys, nervous system, and cardiovascular system, with each system's damage scored as 1 point; a higher total score indicates more severe cumulative damage. Additionally, information on medication use, such as glucocorticoids dosage and hydroxychloroquine use, was documented.

Cognitive Function Assessment

Cognitive function was evaluated by neurologists who had undergone specialized training, using the 2006 Beijing-revised version of the MoCA scale. The MoCA scale assesses seven cognitive domains: visuospatial and executive functions (5 points), naming (3 points), attention and calculation (6 points), language (3 points), abstraction (3 points), delayed recall (5 points), and orientation (6 points), for a total score of 30 points. Testing duration is approximately 10 minutes. To correct for educational level, patients with≤12 years of education and a total scoreless than 30 points receive a +1 point correction to their final total score. A MoCA total score of 26 or higher scale is considered normal and is classified as the non-cognitive dysfunction group, while a total score below 26 indicates cognitive dysfunction.[15]

Serum Indicator Detection

At admission, 4 mL of venous blood was obtained from each patient. Samples were centrifuged at 3800 rpm for 15 minutes with an automated centrifuge (LXJ-IIB; Shanghai Anting Scientific Instrument Factory, China). The upper serum was collected and kept at a low temperature for 35 minutes. The concentrations of IL-6, ICAM-1, and NfL were determined by enzyme-linked immunosorbent assay (ELISA). The ELISA kits were purchased from Shanghai Kebio Biotechnology, China (catalog numbers CB10373-Hu, CB11444-Hu, and CB16117-Hu, respectively).

Observation Indicators

The observation indicators were as follows: (1) an analysis comparing general data between the CD and non-CD groups; (2) analysis of factors influencing cognitive dysfunction in SLE, with observation of odds ratios (OR) and 95% confidence intervals (CI); and (3) predictive value of serum IL-6, ICAM-1, and NfL for cognitive dysfunction in SLE, recording the optimal cut-off values, sensitivity, specificity, area under the curve (AUC), and 95% CI. A combined prediction of cognitive dysfunction was considered if any one of the indicators predicted cognitive dysfunction.

Statistical Analysis

The statistical analyses were carried out using SPSS version 25.0. For normally distributed continuous data, the mean ± standard deviation was calculated, and the independent samples t-test was used for comparison. The measurement data that did not conform to the normal distribution were expressed as median (interquartile range), and the Mann-Whitney U test was used for comparison between groups. Categorical variables were reported as n (%), and intergroup comparisons were performed using the chi-square (χ^2) test. To determine the factors influencing cognitive dysfunction in SLE, we conducted logistic regression analysis. The variance inflation factor (VIF) was used to detect multicollinearity, with the following criteria: VIF<10 indicates no obvious multicollinearity, 10≤VIF<100 indicates moderate multicollinearity, and VIF≥100 indicates severe multicollinearity. Additionally, we constructed Receiver Operating Characteristic (ROC) curves to assess the predictive potential of serum levels of IL-6, ICAM-1, and NfL, both individually and in combination, for cognitive dysfunction in SLE. The criterion for statistical significance was set at a p value lower than 0.05. We adjusted p values for multiple testing to avoid type I errors.

RESULTS

Examining differences in General Data between Individuals with SLE and the Control Group

After conducting the comparison, no statistically meaningful differences were identified between the two

groups in relation to gender, age, body mass index, education degree, and the occurrence of comorbid chronic conditions (p>0.05), thereby confirming the groups' comparability (Table 1).

Contrasting the Serum Biomarker (ICAM-1, IL-6, and NfL) Levels of the SLE Group and the Control Group

In the SLE group, the serum concentrations of ICAM-1, IL-6, and NfL were measured at 154.99 ± 42.94 ng/mL, 22.06 ± 5.05 pg/mL, and 51.88 ± 14.15 pg/mL, respectively. These levels were significantly elevated compared to the control group, which had levels of 65.52 ± 19.46 ng/mL, 9.31 ± 2.35 pg/mL, and 23.18 ± 5.32 pg/mL for the same markers (p<0.05) (Figure 1).

Comparison of Clinical Data and Serum ICAM-1, IL-6, and NfL Levels Between the CD Group and the Non-CD Group

Among the 108 SLE patients, 49 (45.37%) developed cognitive dysfunction. Relative to the non-CD group, individuals in the CD group exhibited elevated serum concentrations of IL-6, ICAM-1, and NfL (p<0.05) (Table 2).

Table 1. Examining differences in general data between individuals with SLE and the control group

Group		SLE group (n=108)	Control group (n=50)	t/χ^2	*p*	95% CI
Age, years		33.95 ± 5.87	32.66 ± 5.74	1.318	0.189	-0.655 to 3.282
Gender, n (%)	Male	36 (33.33)	23 (46.00)	2.344	0.126	
	Female	72 (66.67)	27 (54.00)			
BMI, kg/m²		23.52 ± 1.18	23.19 ± 1.46	1.575	0.117	-0.087 to 0.774
Combined chronic diseases, n (%)	Yes	31 (28.70)	15 (30.00)	0.028	0.868	
	No	77 (71.30)	35 (70.00)			
Education degree, n (%)	Junior high school and below	29 (26.85)	16 (32.00)	4.148	0.126	
	High school/technical secondary school	46 (42.59)	13 (26.00)			
	College or higher	33 (30.56)	21 (42.00)			

BMI: body mass index; CI: confidence interval; SLE: systemic lupus erythematosus.

Table 2. General data of cognitive dysfunction in SLE patients

Factor		CD group (n=49)	Non-CD group (n=59)	t/χ^2	*p*	95% CI
Age, years		34.98 ± 5.58	33.10 ± 6.01	1.670	0.098	-0.351 to 4.107
Gender, n (%)	Male	16 (32.65)	20 (33.90)	0.019	0.891	
	Female	33 (67.35)	39 (66.10)			
Course of disease, years		2.77 ± 0.61	2.65 ± 0.70	0.945	0.347	-0.133 to 0.375
BMI, kg/m²		23.51 ± 1.16	23.54 ± 1.21	0.117	0.907	-0.481 to 0.428
Education degree, n (%)	Junior high school and below	18 (36.73)	15 (25.42)	1.835	0.400	
	High school/technical secondary school	20 (40.82)	26 (44.07)			
	College or higher	11 (22.45)	18 (30.51)			
Family history, n (%)	Yes	19 (38.78)	13 (22.03)	2.827	0.093	
	No	30 (61.22)	46 (77.97)			
Combined chronic diseases, n (%)	Yes	17 (34.69)	14 (23.73)	1.573	0.210	
	No	32 (65.31)	45 (76.27)			
History of SLE, n (%)	Yes	22 (44.90)	19 (32.20)	1.823	0.176	
	No	27 (55.10)	40 (67.80)			
IL-6, pg/mL		24.31 ± 4.24	20.20 ± 4.94	4.593	<0.001	2.339 to 5.892
ICAM-1, ng/mL		171.81 ± 38.22	141.03 ± 41.89	3.955	<0.001	15.351 to 46.213
NfL, pg/mL		56.47 ± 15.17	48.06 ± 12.09	3.206	0.002	3.209 to 13.611
SLEDAI score, score		13.49 ± 2.11	12.86 ± 2.38	1.429	0.156	-0.242 to 1.493
Hydroxychloroquine use, n (%)		32 (65.31)	38 (64.41)	0.009	0.922	
Glucocorticoid dose, mg/d		15.36 ± 4.28	14.82 ± 3.95	1.406	0.163	-0.513 to 3.016
SLICC-DI score, score		1.00(1.00, 2.00)	1.00 (1.00, 1.50)	1.643	0.200	0.188 to 0.203

BMI: body mass index; CD: cognitive dysfunction; CI: confidence interval; ICAM-1: intercellular adhesion molecule-1; IL-6: interleukin-6; NfL: neurofilament light chain; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI: Systemic Lupus International Collaborating Clinics Damage Index.

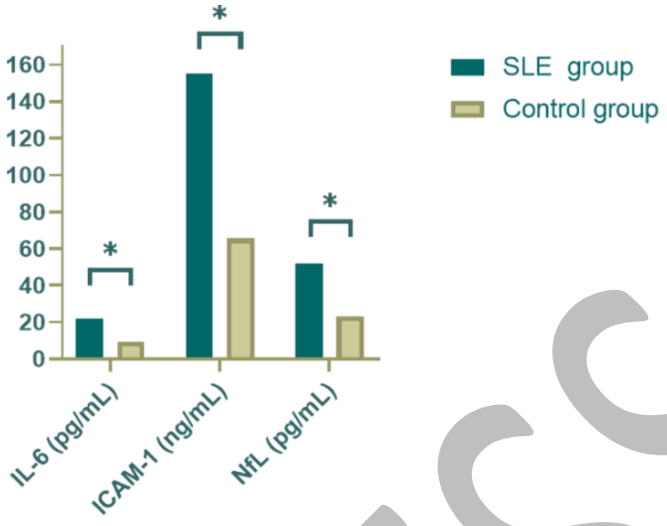

Figure 1. Contrasting the serum biomarker (ICAM-1, IL-6, and NfL) levels of the SLE group and the control group.
[A bar chart showing three sets of bars. Each set compares the mean serum level of a biomarker between the SLE group (n=108) and the Control group (n=50). Error bars indicate standard deviation.]. ICAM-1 (ng/mL): SLE group (154.99) vs. Control group (65.52). *IL-6 (pg/mL): SLE group (22.06) vs. Control group (9.31). *NfL (pg/mL): SLE group (51.88) vs. Control group (23.18). **p(Bonferroni)<0.05. ICAM-1: intercellular adhesion molecule-1; IL-6: interleukin-6; NfL: neurofilament light chain; SLE: systemic lupus erythematosus.

Correlation Between Serum Biomarkers and SLEDAI/SLICC-DI in SLE Patients

Serum ICAM-1 levels correlated positively with SLEDAI scores (r=0.355, p<0.001) but showed no significant association with SLICC-DI scores (r=0.171, p=0.077). Serum IL-6 levels did not correlate significantly with either SLEDAI (r=-0.126, p=0.194) or SLICC-DI (r=-0.130, p=0.182). Similarly, serum NfL levels exhibited no significant correlation with SLEDAI (r=0.025, p=0.798) or SLICC-DI (r=0.005, p=0.956) (Table 3).

Risk Factors for Cognitive Dysfunction in SLE

The multicollinearity test showed that the VIF values of all variables were much lower than the critical value of 10, so it was considered that there was no multicollinearity problem in each variable. Variables that exhibited notable statistical differences in the univariate analysis, namely the levels of IL-6, ICAM-1, and NfL, were selected to serve as independent variables, and the occurrence of cognitive dysfunction in SLE (yes=1, no=0) was used as the dependent variable for logistic regression analysis (variable coding is shown in Table 4). The results showed that levels of IL-6, ICAM-1, and NfL were risk factors for cognitive dysfunction in SLE (p<0.05) (Figure 2).

Predictive Value of Combined Detection of Serological Indicators for Cognitive Dysfunction in SLE

ROC curve analysis showed that the AUC for diagnosing cognitive dysfunction in SLE based on serum levels of IL-6, ICAM-1, and NfL were 0.734 (95% CI, 0.640-0.814), 0.712 (95% CI, 0.617-0.795), and 0.677 (95% CI, 0.580-0.764), respectively. The AUC for combined detection of the three indicators was 0.852 (95% CI, 0.771-0.913), which was significantly higher than that for individual detection (Z=2.771, 3.163, 3.206; p<0.05) (Figure 3, Table 5).

Table 3. Correlation of serum biomarkers with SLEDAI and SLICC-DI in SLE patients

Biomarker	SLEDAI (r, *p*)	SLICC-DI (r, *p*)
IL-6, pg/mL	-0.126, 0.194	-0.130, 0.182
ICAM-1, ng/mL	0.355, <0.001	0.171, 0.077
NfL, pg/mL	0.025, 0.798	0.005, 0.956

ICAM-1: intercellular adhesion molecule-1; IL-6: interleukin-6; NfL: neurofilament light chain; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI: Systemic Lupus International Collaborating Clinics Damage Index.

Table 4. Variable coding table

Variable	Assignment
Cognitive dysfunction occurs	Yes=1, No=0
IL-6	Original value input
ICAM-1	Original value input
NfL	Original value input

ICAM-1: intercellular adhesion molecule-1; IL-6: interleukin-6; NfL: neurofilament light chain.

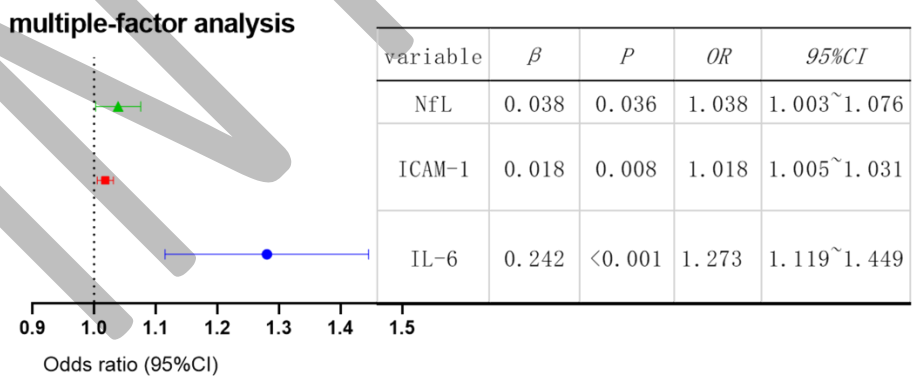

Figure 2. Risk factors for cognitive dysfunction in SLE.
[A forest plot showing the results of a multivariate logistic regression analysis. Three variables are listed on the y-axis: IL-6, ICAM-1, and NfL. The x-axis represents the odds ratio (OR) on a logarithmic scale. Each variable has a point estimate (square) and a 95% confidence interval (horizontal line). IL-6: OR=1.210 (95% CI, 1.081-1.354), *p*=0.001. ICAM-1: OR=1.020 (95% CI, 1.008-1.032), *p*=0.001. NfL: OR=1.055 (95% CI, 1.016-1.095), *p*=0.005. [a]CI: confidence interval; ICAM-1: intercellular adhesion molecule-1; IL-6: interleukin-6; NfL: neurofilament light chain; OR: odds ratio; SLE: systemic lupus erythematosus.

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Table 5. Predictive value of combined detection of serological indicators for cognitive dysfunction in SLE

Variable	Cutoff value	AUC	Sensitivity, % (95% CI)	Specificity, % (95% CI)	*p*	95% CI
IL-6	20.48 pg/mL	0.734	85.7 (72.8-94.1)	55.9 (42.4-68.8)	<0.001	0.640-0.814
ICAM-1	160.8 ng/mL	0.712	67.3 (52.5-80.1)	74.5 (61.6-85.0)	<0.001	0.617-0.795
NfL	52.67 pg/mL	0.677	61.2 (46.2-74.8)	69.5 (56.1-80.8)	0.001	0.580-0.764
Combined prediction		0.852	77.6 (63.4-88.2)	79.7 (67.2-89.0)	<0.001	0.771-0.913

AUC: area under the curve; CI: confidence interval; ICAM-1: intercellular adhesion molecule-1; IL-6: interleukin-6; NfL: neurofilament light chain; SLE: systemic lupus erythematosus.

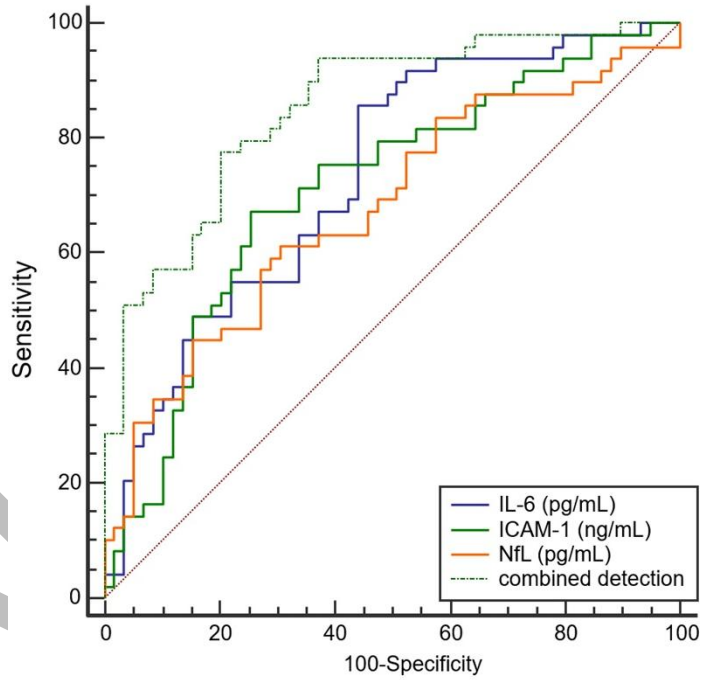

Figure 3. ROC curve for combined detection of serological indicators for cognitive dysfunction in SLE
A graph showing four ROC curves on the same axes. The y-axis is Sensitivity, and the x-axis is 1-Specificity. The four curves represent IL-6, ICAM-1, NfL, and the combined prediction. A diagonal reference line is also shown.
[a]ICAM-1: intercellular adhesion molecule-1; IL-6: interleukin-6; NfL: neurofilament light chain; ROC: receiver operating characteristic.

DISCUSSION

The current European Alliance of Associations for Rheumatology guidelines point out that early diagnosis of SLE is the key to improving prognosis, while NPSLE is often delayed due to insidious presentations. Cognitive function can be used to summarize the psychological changes and functional levels of the examinee's memory, perception, learning, thinking, and emotions. Cognitive dysfunction is a relatively common symptom in patients with SLE.[16] From 40% to 90% of SLE patients will experience neuropsychiatric symptoms, and neuroinflammation plays an important role in the occurrence and development of

neurodegenerative diseases. It can induce or exacerbate the degenerative changes in the nervous system.[17] Therefore, early diagnosis and intervention of cognitive dysfunction in SLE patients are extremely important. There is a large difference in the incidence of cognitive dysfunction in SLE patients reported in the literature,[18,19] which is related to the selected study population, assessment methods, and criteria. This study used two commonly used cognitive function screening scales in the clinic (Mini-Mental State Examination and MoCA) to assess SLE patients. The results showed that among the 108 SLE patients, 49 (45.37%) had cognitive dysfunction, which was lower than the studies by Katz et al[20] and Butt et al.[21] It is considered that the main reasons are the differences in the selected study populations and the different criteria fused to define cognitive dysfunction.

As a core factor in the immune inflammatory response of SLE, IL-6 is associated with cognitive and neuropsychiatric symptoms. The basic research of Trysberg et al[22] and the recent research of Balajkova et al[23] have confirmed that there is a direct biological connection between IL-6 and the neuronal injury marker NfL in the cerebrospinal fluid of NPSLE patients. Previous studies have pointed out that inflammatory responses and oxidative stress are closely related to cognitive impairment. During brain injury, inflammatory responses and oxidative stress occur, and these two changes can lead to the production and deposition of β-amyloid. Once β-amyloid abnormally accumulates, it can cause neuronal deformities and induce cognitive dysfunction. Furthermore, the accumulation of abundant inflammatory factors and oxidative stress mediators might induce abnormal neurotransmitter secretion, directly contributing to cognitive impairment.[24] This study found that there were differences in the levels of serum IL-6 between SLE patients with and without CD. In addition, in this study, serum ICAM-1 levels were significantly positively correlated with SLEDAI scores but showed no significant correlation with SLICC-DI scores, suggesting that elevated ICAM-1 was associated with SLE activity and may reflect active central nervous system lupus. There was no significant correlation between serum IL-6 level, NfL level, and SLEDAI score or SLICC-DI score. The results may be related to the smaller sample size or the need for more specific central nervous system indicators. Multivariate logistic regression analysis showed that the levels of serum IL-6, ICAM-1, and NfL are influencing factors for cognitive dysfunction in SLE. The reason is analyzed as follows: IL-6, as a pro-inflammatory cytokine, can directly stimulate the nervous system in the body, leading to abnormal secretion of neurotransmitters, directly damaging brain cognitive function, and inducing the occurrence of cognitive dysfunction.[25] The study by Suntoko et al[26] also found that the level of IL-6 in SLE patients was negatively correlated with the MoCA score, which directly confirmed the correlation between IL-6 and cognitive function in SLE patients. Previous studies have shown that IL-6 can activate the Janus kinase (JAK)/signal transducer and activator of transcription 3 (*STAT3)* pathway to promote neuroinflammation,[26] while JAK inhibitors (e.g., tofacitinib) have been shown to reduce IL-6 levels and improve some neuropsychiatric symptoms in SLE patients,[27] suggesting that targeting the IL-6 pathway may alleviate cognitive impairment.

In addition, this study also found that serum ICAM-1 and NfL levels were influencing factors of cognitive dysfunction in SLE. Serum ICAM-1 is a member of the immunoglobulin superfamily and is highly expressed in vascular endothelial cells. The increase in ICAM-1 may exacerbate cerebral blood flow perfusion insufficiency and inflammatory responses, damage the integrity of the blood-brain barrier, and thereby affect cognitive function.[28] In addition, several studies have confirmed that serum NfL can be used as a biomarker for neuronal damage in NPSLE patients.[29,30] However, neither Ahmadzade et al[31] nor Zervides et al[32] found significant differences in serum or plasma NfL levels between NPSLE patients and non-NPSLE patients. It may be due to the differences in sample selection, detection methods, and statistical analysis in different studies, suggesting that the specificity of NfL as a biomarker of cognitive dysfunction fluctuates in different studies, and further research is needed to clarify its role in SLE cognitive dysfunction. NfL is a component of neurofilaments, and neurofilaments are structural parts of neuronal axons, reflecting the level of neuronal and axonal damage. NfL is released into the extracellular space and enters the peripheral blood through the blood-brain barrier. The increase in its peripheral blood level reflects the degree of neuronal damage in the brain. Cognitive function depends on an intact neuronal network, and changes in NfL levels can predict the development of cognitive dysfunction.[33] Some studies have reported that elevated NfL levels can cause

neuronal loss, cortical thinning, and neurodegenerative changes, affecting cognitive function.[34] In addition, studies by Benkert[35] and Karantali[36] have found that patients with multiple sclerosis (an autoimmune disease associated with demyelination and neurodegeneration) and frontotemporal dementia have significantly increased serum NfL levels, which are related to the exacerbation of disease activity in multiple sclerosis and the increased degree of cognitive impairment in patients with frontotemporal dementia. The pathogenesis of NfL involvement in SLE combined with cognitive dysfunction is not clear. It is analyzed that the possible mechanism is that after SLE involves the central nervous system, axonal damage causes abnormal aggregation of NfL in neurons and axons, failure of transport, and axonal degeneration, leading to axonal and neurofibrillary atrophy, and then causing signal transduction damage and neuronal dysfunction.[37]

The results of ROC curve analysis indicated that the AUCs for identifying cognitive dysfunction in SLE patients, based on serum concentrations of IL-6, ICAM-1, and NfL, were 0.734 ,0.712 and 0.677, respectively. The AUC for combined diagnosis of the three indicators was 0.852, which was markedly superior to that for individual detection. This indicates that the combination of the three can effectively improve the predictive value for cognitive dysfunction in SLE. The reason is analyzed as follows: combined diagnosis can overcome the shortcomings of insufficient sensitivity or specificity of individual indicators, providing a more comprehensive and accurate assessment of the patient's condition. Compared with a single indicator, the combination can reduce the occurrence of missed and misdiagnoses, improving the accuracy of diagnosis. Certainly, this study also has several limitations. Its cross-sectional design only allows us to examine associations between serum biomarkers and CD rather than establish causality. The relatively small sample size may introduce bias, and the absence of follow-up data precludes assessment of these markers' utility for predicting long-term CD progression. Additionally, cognitive impairment was evaluated solely with the MoCA scale, whose subjective nature cannot be fully excluded. Furthermore, we did not measure SLE-specific autoantibodies closely linked to neuropsychiatric manifestations (e.g., anti-dsDNA, anti-NR2) nor include cerebrospinal fluid biomarkers that could provide more direct evidence of central nervous system pathology. Future large-scale, multicenter longitudinal studies should integrate serum markers, autoantibody profiles, and cerebrospinal fluid indicators to achieve a more comprehensive predictive analysis, thereby improving early recognition and mechanistic understanding of cognitive dysfunction in SLE.

In summary, serum levels of IL-6, ICAM-1, and NfL in SLE patients are closely related to the occurrence of cognitive dysfunction. The combined detection of these three markers demonstrates high diagnostic efficiency for cognitive dysfunction, which can provide an objective serological basis for the early identification of cognitive dysfunction in SLE patients and lay a foundation for clinical routine early intervention in rheumatology. It also provides a reference for cognitive assessment and marker research in the field.

STATEMENT OF ETHICS

This study was approved by the ethics committee of Hebei General Hospital(2025-LW-0163). Written informed consent was obtained from all participants before recruitment.

FUNDING

Medical Science Research Project of Hebei Province, (No. 20190361).

CONFLICT OF INTEREST

The authors affirm that they do not have any financial conflicts of interest or personal relationships that could have appeared to influence the work reported in this manuscript.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

The datasets (No. GSE87466, GSE16879 and GSE13367) generated and/or analysed during the current study are available in the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/).

AI ASSISTANCE DISCLOSURE

In the preparation of this manuscript, artificial intelligence (AI) tools (e.g., Grammarly, ChatGPT) were used solely for language polishing. AI tools did not participate in any core research processes, including study design, data collection, statistical analysis, result interpretation, or conclusion drafting. All content related to the research core and academic integrity was independently completed by the authors.

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