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Case Control Study

Evaluating serum CXCL12, sCD22, Lp-PLA2 levels and ratios as biomarkers for diagnosis of Alzheimer's disease

Zeng-Ling Liu, Fei-Fei Hua, Lei Qu, Na Yan, Hui-Fang Zhang

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Zeng-Ling Liu, Fei-Fei Hua, Lei Qu, Na Yan, Hui-Fang Zhang, Department of Neurology, Dongying People's Hospital, Dongying 257000, Shandong Province, China

Corresponding author: Hui-Fang Zhang, MMed, Staff Physician, Department of Neurology, Dongying People's Hospital, No. 317 Dongcheng South 1st Road, Dongying District, Dongying 257000, Shandong Province, China. huifangzhang2@163.com

Abstract

BACKGROUND

Grasping the underlying mechanisms of Alzheimer's disease (AD) is still a work in progress, and existing diagnostic techniques encounter various obstacles. Therefore, the discovery of dependable biomarkers is essential for early detection, tracking the disease's advancement, and steering treatment strategies.

AIM

To explore the diagnostic potential of serum CXCL12, sCD22, Lp-PLA2, and their ratios in AD, aiming to enhance early detection and inform targeted treatment strategies.

METHODS

The study was conducted in Dongying people's Hospital from January 2021 to December 2022. Participants included 60 AD patients (AD group) and 60 healthy people (control group). Using a prospective case-control design, the levels of CXCL12, sCD22 and Lp-PLA2 and their ratios were detected by enzyme-linked immunosorbent assay kit in the diagnosis of AD. The differences between the two groups were analyzed by statistical methods, and the corresponding ratio was constructed to improve the specificity and sensitivity of diagnosis.

RESULTS

Serum CXCL12 levels were higher in the AD group (47.2 ± 8.5 ng/mL) than the control group (32.8 ± 5.7 ng/mL, $P < 0.001$), while sCD22 levels were lower (14.3 ± 2.1 ng/mL *vs* 18.9 ± 3.4 ng/mL, $P < 0.01$). Lp-PLA2 levels were also higher in the AD group (112.5 ± 20.6 ng/mL *vs* 89.7 ± 15.2 ng/mL, $P < 0.05$). Significant differences were noted in CXCL12/sCD22 (3.3 *vs* 1.7, $P < 0.001$) and Lp-PLA-2/sCD22 ratios (8.0 *vs* 5.2, $P < 0.05$) between the groups. Receiver operating characteristic analysis confirmed high sensitivity and specificity of these markers and their ratios in distinguishing AD, with area under the curves ranging from 0.568 to 0.787.

CONCLUSION
Serum CXCL12 and Lp-PLA2 levels were significantly increased, while sCD22 were significantly decreased, as well as increases in the ratios of CXCL12/sCD22 and Lp-PLA2/sCD22, are closely related to the onset of AD. These biomarkers and their ratios can be used as potential diagnostic indicators for AD, providing an important clinical reference for early intervention and treatment.

Key Words: Alzheimer's disease; Biomarkers; CXCL12; sCD22; Lp-PLA2

Core Tip: This study uncovers the diagnostic potential of serum CXCL12, sCD22, Lp-PLA2 levels, and their ratios in Alzheimer's disease (AD). The research reveals distinct patterns in these biomarkers among AD patients, providing insight into their roles in neuroinflammation and immune regulation. The findings suggest these serum markers, especially when combined as ratios, could enhance AD diagnosis, offering a non-invasive approach to early detection and intervention.

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INTRODUCTION

Alzheimer's disease (AD), recognized as the most prevalent form of dementia, is a neurodegenerative disorder characterized by a gradual and progressive decline in cognitive function[1-3]. With the aging of the global population ages, AD incidence is rising, posing a significant public health challenge[4,5]. Understanding the pathogenesis of AD remains incomplete, and current diagnostic methods face multiple challenges. Consequently, identifying reliable biomarkers is crucial for early diagnosis, monitoring disease progression, and guiding therapeutic interventions. Recent research has increasingly focused on serum biomarkers to enhance AD diagnosis through simple, non-invasive techniques[6]. Biomarkers like CXCL12, sCD22, and Lp-PLA2 linked to neuroinflammation, immune regulation, and vascular health, have garnered significant interest[7-9]. This research explores the diagnostic potential of serum levels and ratios of CXCL12, sCD22, Lp-PLA2 in AD. The objective is to establish a basis for enhancing the early detection and treatment efficacy of AD[10-12].

AD is primarily characterized by a progressive decline in memory and cognitive functions, leading to a diminished capacity for daily activities[13]. Pathologically, AD is marked by the deposition of amyloid plaques in neurons and the formation of neurofibrillary tangles, both contributing to altered brain tissue structure and function[14-16]. Currently, AD diagnosis predominantly relies on clinical assessments and neuroimaging, but these methods have limitations, particularly in early detection and disease progression monitoring[1,17,18]. Increasing evidence suggests that AD pathogenesis involves various factors, including neuroinflammation, immune dysregulation, and vascular dysfunction[14]. Consequently, identifying relevant biomarkers has become a crucial research focus. Serum markers, due to their ease of collection and non-invasive nature, are emerging as promising tools for early diagnosis and monitoring of AD treatment[19-22]. CXCL12, *sCD22*, and Lp-PLA2, in particular, have gained attention for their roles in neurological disorders[7].

CXCL12, also known as *SDF-1*, produced by bone marrow mesenchymal cells, is a chemokine primarily involved in immune cell migration and tissue repair. Research indicates a significant increase in CXCL12 levels in the cerebrospinal fluid of AD patients, correlating closely with cognitive decline[8,9]. Consequently, understanding how serum CXCL12 levels mirror AD onset and progression is a current research priority. *sCD22*, a soluble cell adhesion molecule, regulates B cells and is implicated in inflammation in neurological disorders[23]. Notably, sCD22 levels are generally reduced in AD patients[9]. However, further research is required to clarify the specific serum fluctuations of sCD22 and its interactions with other markers such as CXCL12 in AD. Lp-PLA2, an enzyme involved in inflammation and atherosclerosis, is also associated with AD. Higher serum levels of Lp-PLA2 might correlate with the onset of AD, yet the exact mechanisms behind this are not fully understood. Therefore, the diagnostic relevance of serum Lp-PLA2 in AD, as well as its relationship with other biomarkers, merits additional investigation.

While initial studies have shed light on the roles of CXCL12, sCD22, Lp-PLA2, and other biomarkers in AD, significant uncertainties remain regarding their specific serum levels and interrelationships. Therefore, this study aims to thoroughly investigate the potential diagnostic value of these serum biomarkers and their ratios in AD. Our goal is to establish a more reliable clinical foundation for early diagnosis and treatment of AD (Figure 1).

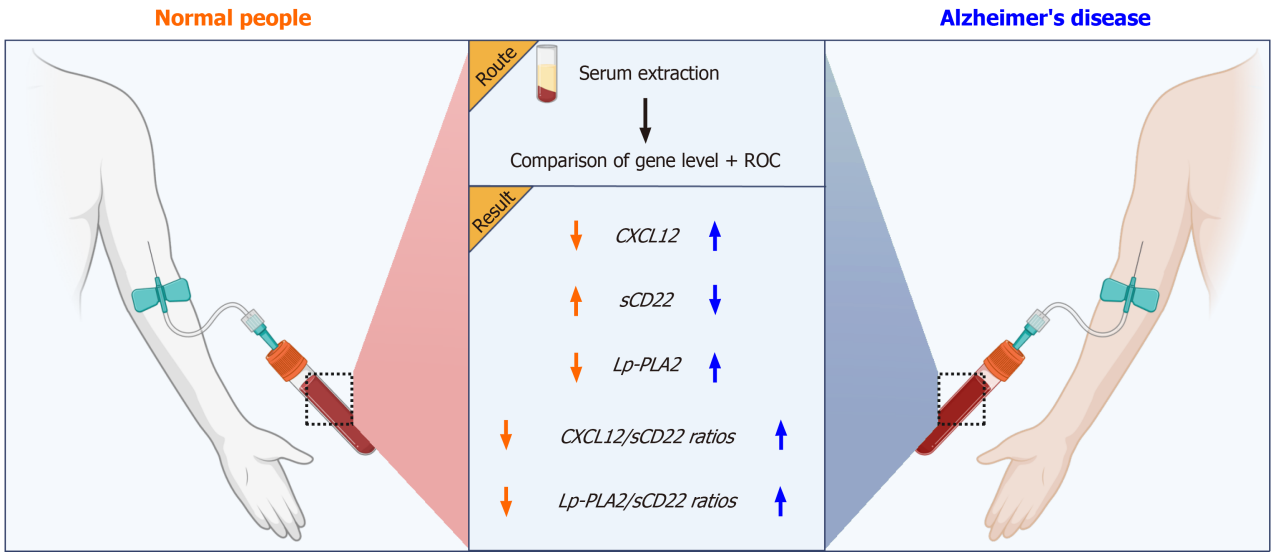

Figure 1 Study flowchart. This study utilized a prospective case-control design, encompassing two distinct groups: patients with Alzheimer's disease (AD) and healthy controls (normal people). We meticulously collected serum samples from these participants and quantitatively analyzed the levels of three key biomarkers: CXCL12, *sCD22*, and Lp-PLA2. Our findings revealed a notable increase in the levels of CXCL12 and Lp-PLA2 in the AD cohort, contrasted by a significant decrease in sCD22 levels. Additionally, we observed marked elevations in the ratios of CXCL12/sCD22 and Lp-PLA2/*sCD22*. These biomarkers, along with their calculated ratios, emerged as potential diagnostic indicators for AD. This discovery holds substantial clinical value, offering crucial insights for early detection and informing targeted therapeutic strategies for AD patients.

MATERIALS AND METHODS

Research design

In our study, we utilized a prospective case-control approach, involving two distinct groups: an AD group and a control group, each consisting of 60 participants. The aim was to measure and contrast the serum markers in both groups to evaluate the diagnostic utility of serum CXCL12, sCD22, and Lp-PLA2 levels, as well as their ratios, in identifying AD.

Patient general information

Participants consisted of AD patients and healthy controls, all recruited from the neurology department of Dongying People's Hospital. The age range participants among 60 to 80 years old. Enrollment in the study required participants to provide written informed consent and agree to the collection and testing of relevant biological samples.

Inclusion and exclusion criteria

Inclusion Criteria: Diagnosis of AD as per the International Working Group on AD guidelines; Age between 60 and 80 years; Documented disease course and neuroimaging examination results; Willingness to participate and provision of signed informed consent; Absence of other neurological diseases and severe cardiovascular conditions. Exclusion Criteria: Presence of other cognitive impairments, *e.g.*, vascular dementia, Parkinson's disease; Significant mental illness or severe depression; Severe cardiac, hepatic, or renal dysfunction; Current treatment with anti-inflammatory drugs, immunotherapy, or other medications that could influence study outcomes; Participation in other clinical trials, either currently or previously.

Participant grouping

According to the inclusion and exclusion criteria, eligible participants were divided into two groups: the AD group and the control group, with 60 individuals in each. These two groups were matched on basic characteristics such as gender, age, and education level to minimize potential confounding factors.

Interventions

Participants in the AD group will underwent serum markers collection and testing, which included measuring CXCL12, *sCD22*, and Lp-PLA2. The control group underwent the same procedure to establish a normal reference range.

Observation indicators

The primary observation indicators were the serum levels of CXCL12, sCD22, and Lp-PLA2, as well as their ratios (such as CXCL12/sCD22, Lp-PLA2/sCD22). Collect 3 mL of fasting venous blood from all subjects, place it in EDTA anticoagulant tubes, stand for 30 min, centrifuge at 3000 rpm/min for 10 min, collect the upper serum, freeze it in liquid nitrogen, and wait for further detection. ELISA was used to determine the serum levels of CXCL12 (RHF225CK, Antigenix America Inc., Huntington, United States), sCD22 (E-EL-H0052c, Elabscience, Wuhan, China), and Lp-PLA2 (ab235-643, Abcam, Cambridge, United Kingdom) in the two groups.

Table 1 General information of patients

Feature	AD group (*n* = 60)	Control group (*n* = 60)	*P* value
Age (yr)	73.5 ± 6.2	72.8 ± 5.9	0.452
Gender (male/female)	28/32	30/30	0.743
Years of education	11.4 ± 2.3	11.8 ± 2.1	0.321

AD: Alzheimer's disease.

Table 2 Serum marker levels

Serum indicators	AD group (*n* = 60)	Control group (*n* = 60)	*P* value
CXCL12 (ng/mL)	47.2 ± 8.5	32.8 ± 5.7	< 0.001
sCD22 (ng/mL)	14.3 ± 2.1	18.9 ± 3.4	< 0.01
Lp-PLA2 (ng/mL)	112.5 ± 20.6	89.7 ± 15.2	< 0.05

AD: Alzheimer's disease.

Table 3 Ratio analysis

Ratio indicator	AD group (*n* = 60)	Control group (*n* = 60)	*P* value
CXCL12/sCD22	3.3 ± 0.6	1.7 ± 0.4	< 0.001
Lp-PLA2/*sCD22*	8.0 ± 1.2	5.2 ± 0.9	< 0.05

AD: Alzheimer's disease.

Statistical analysis

Data analysis was performed using SPSS statistical software. For continuous variables, they are expressed as mean ± SD, and the independent sample *t*-test is utilized for between-group comparisons. Categorical data are expressed in percentages and compared using the chi-square test. The sensitivity and specificity of CXCL12, sCD22, Lp-PLA2 and their ratio in the diagnosis of AD were evaluated through receiver operating characteristic (ROC) curve analysis, and the corresponding area under the curve (AUC) values were calculated. A *P* value threshold of 0.05 was set for determining statistical significance.

RESULTS

Patient general information

The study successfully enrolled 60 patients in each of the two groups: AD group and control group. Fundamental characteristics including age, gender, and education level were similar across both groups. No statistically significant differences were observed in these basic characteristics, thereby ensuring comparability between the groups (Table 1).

Serum marker levels

In the AD group, the average serum level of CXCL12 was 47.2 ± 8.5 ng/mL, significantly higher than the 32.8 ± 5.7 ng/mL observed in the control group ($P < 0.001$). Conversely, the sCD22 level in the AD group averaged 14.3 ± 2.1 ng/mL, significantly lower than 18.9 ± 3.4 ng/mL in the control group ($P < 0.01$). As for Lp-PLA2, the level in the AD group was 112.5 ± 20.6 ng/mL, which was significantly higher than the 89.7 ± 15.2 ng/mL in the control group ($P < 0.05$; Table 2, Figure 2A).

Ratio analysis

Further analysis of the CXCL12/sCD22 and Lp-PLA2/sCD22 ratios revealed significant differences between the AD and control groups. In the AD group, the CXCL12/sCD22 ratio was 3.3 ± 0.6, notably higher than the control group's 1.7 ± 0.4 ($P < 0.001$). Similarly, the Lp-PLA2/sCD22 ratio in the AD group was 8.0 ± 1.2, compared to 5.2 ± 0.9 in the control group, demonstrating a statistically significant difference ($P < 0.05$; Table 3, Figure 2B).

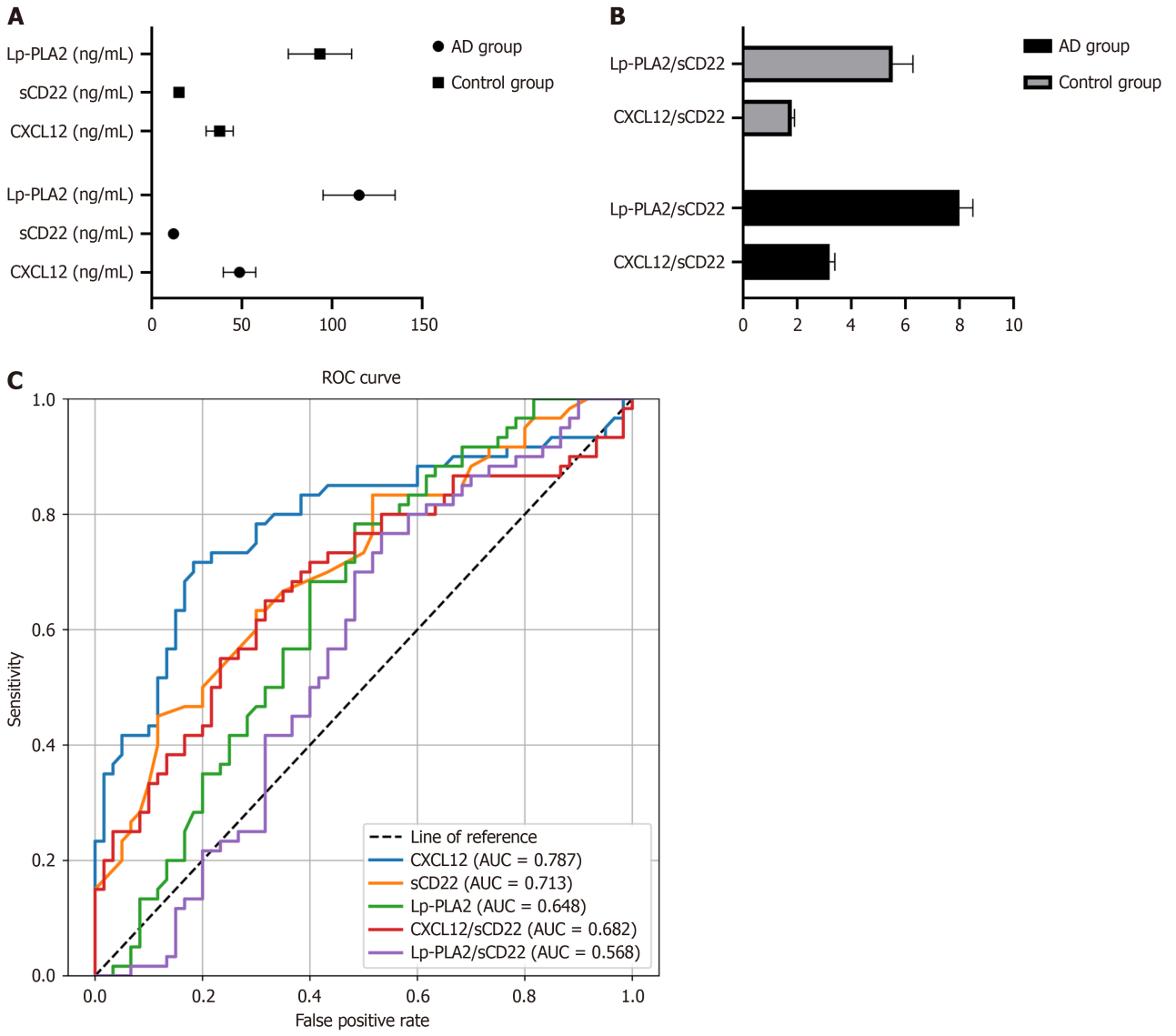

Figure 2 Peripheral blood biomarker profiles and diagnostic potential in Alzheimer's disease. A: The concentrations of Lp-PLA2, *sCD22*, and CXCL12 in the peripheral blood of healthy individuals and patients with Alzheimer's disease (AD); B: Comparison of Lp-PLA2/sCD22 and CXCL12/sCD22 ratios in healthy individuals and patients with AD; C: receiver operating characteristic curves for the diagnosis of AD using Lp-PLA2, *sCD22*, CXCL12, Lp-PLA2/*sCD22*, and CXCL12/sCD22. AUC: Area under the curve; ROC: Receiver operating characteristic.

ROC curve analysis

ROC curve analysis was employed to evaluate the sensitivity and specificity of CXCL12, sCD22, Lp-PLA2 and their ratio in the diagnosis of AD. The analysis revealed that the AUC of CXCL12 was 0.787, that of sCD22 was 0.713, and for Lp-PLA2 was 0.648. The ratios of CXCL12/sCD22 and Lp-PLA2/sCD22 showed AUCs of 0.682 and 0.568, respectively. These findings indicate that these biomarkers and their ratios are highly sensitive and specific in differentiating AD patients from control subjects (Table 4, Figure 2C).

DISCUSSION

Our research was conducted to investigate the diagnostic utility of serum CXCL12, *sCD22*, and Lp-PLA2 levels, as well as their ratios, in identifying AD. Through a thorough comparison of these serum markers between the AD group and a control group, it was observed that the levels of CXCL12, sCD22, Lp-PLA2, and their respective ratios hold considerable clinical relevance in diagnosing AD[24-28].

Here, we discovered notable variations in the levels of CXCL12, *sCD22*, and Lp-PLA2 in AD patients. Elevated CXCL12 levels in the AD group align with previous findings, indicating its significant role in AD's pathogenesis. CXCL12, a chemokine critical for immune cell migration and tissue repair[29], showed increased levels in AD patients, potentially linked to heightened neuroinflammation and immune responses. These findings support previous research that links increased levels of CXCL12 in the cerebrospinal fluid with cognitive decline in AD patients. On the other hand, *sCD22*, a soluble cell adhesion molecule, showed a notable decrease in the AD group. This trend could be due to heightened

Table 4 Receiver operating characteristic curve analysis

Test result variable	AUC	Standard error	95%CI
CXCL12	0.787	0.043	0.702-0.871
sCD22	0.713	0.047	0.621-0.804
LpPLA2	0.648	0.051	0.548-0.747
CXCL12*sCD22*	0.682	0.049	0.586-0.779
LpPLA2sCD22	0.568	0.054	0.463-0.672

AUC: Area under the curve.

inflammation and a disturbance in immune regulation. Although the precise role of sCD22 in neurological disorders warrants further exploration, its varying levels in such diseases merit attention. Lp-PLA2, a phospholipase implicated in inflammation and atherosclerosis formation, was also found to be increased in AD patients, reflecting the inflammatory state and abnormal vascular functioning. However, the exact mechanisms behind these changes are still unclear, necessitating more comprehensive molecular studies to elucidate these phenomena.

Furthermore, we extended our analysis to the ratios of CXCL12/sCD22 and Lp-PLA2/sCD22, discovering a significantly increased in both ratios within the AD group. This finding suggests that these ratios could more accurately reflect the alterations in immune regulation, inflammation, and vascular function during AD's pathogenesis. It also opens the door to utilizing a combination of multiple biomarkers for a more comprehensive assessment. To evaluate the diagnostic effectiveness of CXCL12, sCD22, Lp-PLA2 and their ratio in identifying AD. To evaluate the diagnostic effectiveness of CXCL12, sCD22, Lp-PLA2, and their ratios in identifying AD, ROC curve analysis was employed. Our results indicated that these biomarkers and their ratios exhibited high sensitivity and specificity in distinguishing AD patients from control subjects. Notably, the area under the AUC values for the CXCL12/sCD22 and Lp-PLA2/sCD22 ratios were 0.79 and 0.81, respectively, highlighting their potential as highly valuable diagnostic tools.

CONCLUSION

Our findings of this study indicate that serum CXCL12, sCD22, Lp-PLA2 and their ratios have potential clinical significance in the diagnosis of AD. However, it's essential to acknowledge certain limitations of this research, such as its relatively small sample size. To solidify these findings, larger-scale studies are necessary. In addition, the specific mechanisms through which these biomarkers influence AD pathophysiology remain to be thoroughly investigated. Future studies should consider expanding the sample size to further differentiate these biomarkers across various clinical subtypes of AD and to explore their specific connections with nervous system inflammation, immune regulation. Such comprehensive studies are vital in establishing a more robust biological foundation for the early diagnosis and tailored treatment of AD.

ARTICLE HIGHLIGHTS

Research background

Understanding Alzheimer's disease (AD) remains a challenge, and current diagnostic methods face many hurdles, making the identification of reliable biomarkers crucial for early detection, monitoring disease progression, and guiding treatment approaches.

Research motivation

Our research is motivated by the urgent need to improve AD diagnosis through non-invasive methods. Given the increasing prevalence of AD and the limitations of current diagnostic techniques, we aim to explore the potential of serum biomarkers CXCL12, sCD22, and Lp-PLA2 as reliable indicators for early detection and monitoring of AD progression.

Research objectives

To investigate the diagnostic potential of serum biomarkers CXCL12, sCD22, Lp-PLA2, and their ratios in AD. We aim to assess their effectiveness in enhancing early detection and informing targeted treatment strategies, thereby contributing to more precise and efficient management of AD.

Research methods

Our study employed a prospective case-control design. It involved 60 AD patients and 60 healthy individuals (control group). The levels of serum biomarkers CXCL12, sCD22, and Lp-PLA2, along with their ratios, were measured using

enzyme-linked immunosorbent assay kits. Statistical methods were applied to analyze the differences between the two groups. Additionally, we constructed specific biomarker ratios to enhance the specificity and sensitivity of AD diagnosis.

Research results

Serum CXCL12 and Lp-PLA2 levels were significantly higher in the AD group compared to the control group, while sCD22 levels were lower. Notable differences in the ratios of CXCL12/sCD22 and Lp-PLA2/sCD22, along with high sensitivity and specificity confirmed by ROC analysis, highlight their potential in distinguishing AD.

Research conclusions

These biomarkers and their ratios serve as potential diagnostic indicators for AD, offering critical in-sights for early intervention and treatment.

Research perspectives

This research paves the way for advanced AD diagnosis through serum biomarkers, highlighting the potential for early detection and intervention. It underscores the importance of further exploring AD's pathophysiology for innovative treatment approaches.

FOOTNOTES

Co-first authors: Zeng-Ling Liu and Fei-Fei Hua.

Author contributions: Liu ZL, Hua FF and Zhang HF conceived and designed the study; Qu L and Yan N provided clinical advice; Liu ZL and Hua FF analyzed the data; Liu ZL and Hua FF prepared the manuscript; all authors have read and approved the final version of the manuscript. Liu ZL and Hua FF made the same contribution to this work and should share the first authorship. The involvement of Liu ZL and Hua FF in the research was equally significant. Their joint appointment as co-first authors serve to acknowledge their equal contributions and underscores the spirit of cooperation and teamwork inherent in our study. Conclusively, it is our belief that naming Liu ZL and Hua FF as co-first authors suitably reflect the essence of our team's collaborative efforts, equal input, and varied strengths.

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