MEDS Basic Medicine (2025)
Clausius Scientific Press, Canada

DOI: 10.23977/medbm.2025.030118
ISSN 2616-2091 Vol. 3 Num. 1

The Value of Combined Detection of Blood Biomarkers in Early Diagnosis and Clinical Application of Alzheimer's Disease

Yiyang Li, Meichen Liu*, Meng Zhang, Yang Yu, Yankui Shi

Laboratory Department, Affiliated Hospital of Hebei University, Baoding, Hebei, 071000, China
**Corresponding author*

Keywords: Alzheimer's Disease; Blood Biomarkers; Combined Detection; Early Diagnosis; Clinical Application

Abstract: Alzheimer's Disease (AD) is the most common cause of dementia in the elderly, placing a significant burden on society and families. Early and accurate diagnosis is crucial for slowing disease progression, improving patients' quality of life, and reducing the burden on caregivers. Blood biomarker testing, as an emerging diagnostic method, offers non-invasive, convenient, and efficient advantages. This article reviews the types of blood biomarkers, their clinical significance, and the value of combined testing in the early diagnosis and clinical application of Alzheimer's Disease, while also discussing existing challenges and future directions for development.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that has become a serious global public health issue. Currently, there is no specific treatment available, and early diagnosis is crucial for slowing disease progression. Traditional diagnostic methods, such as cognitive scale assessments, imaging tests (PET, CT/MRI), and cerebrospinal fluid analyses, have numerous limitations. However, the combined detection of blood biomarkers is expected to become an ideal early diagnostic tool.

2. Epidemiology and burden of Alzheimer's disease

According to the "China Alzheimer's Disease Report 2024" [1], China has a large number of Alzheimer's disease patients, with the number expected to reach 40 million by 2050. The economic burden is significant, with the annual cost reaching 1.6 trillion yuan. On average, patients face an annual economic burden of 150,000 yuan per person. Alzheimer's disease has become the fifth leading cause of death in China.

3. Limitations of traditional alzheimer's disease diagnosis methods

3.1. Cognitive scale assessment

Advantages: economical;
Disadvantages: the results are subjective, affected by the patient's education level, and take a long time.

3.2. Conventional imaging examination (MRI, CT)

Advantages: It can clearly image brain tissue;
Disadvantages: It is not specific and cannot distinguish cognitive dysfunction caused by other diseases.

3.3. Molecular imaging examination (Aβ-PET, Tau-PET, FDG-PET)

Advantages: It can display the distribution of Aβ in brain, semi-quantitative, which is helpful to early diagnosis;
Disadvantages: high cost, low accessibility, lack of specificity of FDG-PET.

3.4. Cerebrospinal fluid marker detection (Aβ42/Aβ40, Tau, P-Tau)

Advantages: high specificity and sensitivity;
Disadvantages: hospitalization for puncture is required, and patients have poor compliance.

4. Application of blood biomarkers in the diagnosis of Alzheimer's disease

4.1. βamyloid (Aβ)

Aβ is a metabolic product of the human brain, derived from the β-amyloid precursor protein (APP) through the action of γ-secretase and β-secretase. The primary forms of Aβ are Aβ40 and Aβ42, with Aβ42 being particularly hydrophobic, which makes it prone to form oligomers and exhibit neurotoxicity. In disease states, the imbalance between Aβ production and clearance leads to abnormal secretion and accumulation, resulting in pathological deposition of Aβ. The plasma Aβ42/Aβ40 ratio is more valuable for detecting brain Aβ pathology compared to a single Aβ42 level. Patients with AD who test positive for Aβ pathology have lower levels of Aβ42 and Aβ42/Aβ40 in their plasma compared to those who are negative.

4.2. Phosphorylated Tau protein (p-Tau)

Excessive phosphorylation reduces the Tau protein's ability to bind to microtubules, leading to the shedding of Tau proteins that aggregate into oligomers and paired helical filaments, ultimately forming neurofibrillary tangles. The loss of Tau protein function leads to microtubule instability and a reduction in axonal transport, potentially causing neuropathy and clinical symptoms [3]. Phosphorylated Tau proteins, such as p-Tau181, p-Tau217, and p-Tau231, show good diagnostic efficacy in Alzheimer's disease (AD). The diagnostic performance of plasma p-Tau is comparable to that of cerebrospinal fluid and PET, with an AUC of 0.96[4].

4.3. Neurofilin (NFL)

NFL is a key marker of axonal damage and serves as an ideal prognostic indicator for assessing the severity of neurodegeneration in AD patients. An increase in NFL levels in the blood reflects the severity of brain atrophy, metabolic insufficiency, and decreased white matter integrity[3]. In individuals with no cognitive impairment, the relationship between baseline blood NFL levels and subsequent neurodegenerative changes is more pronounced in those with high Aβ loads.

4.4. Glial fibrillary acidic protein (GFAP)

GFAP is a specific protein of astrocytes. Astrocyte proliferation is one of the potential driving factors of AD pathology and also an early sensitive marker of AD and neuroinflammation [3]. Studies have shown that plasma GFAP levels can assist in judging the neuroinflammatory state during AD pathology.

5. The value of combined detection of blood biomarkers

5.1. Improve diagnostic efficacy

The combined detection of multiple indicators can improve the diagnostic efficacy and accuracy of suspected AD patients. Combined detection of Aβ and p-tau can reflect more comprehensively

The pathological process of AD can reduce the false negative or false positive results that may occur when testing for a single marker. For example, testing for Aβ42/Aβ40, p-Tau181, and p-Tau217 simultaneously can more accurately determine whether a patient has Aβ pathology or Tau pathology, thereby improving the accuracy of early diagnosis.

5.2. Early prediction and risk assessment

By jointly testing blood biomarkers, potential AD patients can be identified in the early stages of the disease, even before clinical symptoms appear. For individuals with a family history of AD, carrying susceptible genes, or other risk factors, regular joint testing of blood biomarkers can help predict the risk of disease onset early, allowing for timely intervention to slow disease progression.

5.3. Disease surveillance and prognosis assessment

In the treatment of AD patients, the combined detection of blood biomarkers can be used to monitor disease progression and treatment effectiveness. For example, by dynamically observing changes in NFL levels, the extent of neuronal degeneration or damage can be assessed, and the disease's progression can be evaluated. Additionally, combining the detection of inflammatory markers like GFAP can help determine the state of neuroinflammation during treatment, providing a basis for adjusting the treatment plan.

6. Existing problems and challenges

6.1. Testing technology and standardization issues

At present, there are various blood biomarker detection methods, and there are some differences between different detection technologies. Moreover, there is a lack of unified standardized detection process and quality control standards. This may affect the comparability and repeatability of the detection results, which limits its wide promotion in clinical application.

6.2. The specificity and sensitivity of biomarkers need to be improved

Although some blood biomarkers have shown good performance in the diagnosis of Alzheimer's disease (AD), they still have certain limitations. Some markers may also show abnormalities in other neurological conditions, leading to insufficient specificity; while others may lack sufficient sensitivity in the early stages of the disease, potentially missing the optimal time for diagnosis and intervention. Therefore, further research is needed to identify blood biomarkers with higher specificity and sensitivity.

6.3. Insufficient accumulation of clinical samples and data

The application of combined detection of blood biomarkers in the diagnosis of Alzheimer's disease is still in the development and validation phase, requiring substantial clinical samples and data. Currently, the sample sizes for related studies are relatively limited, and there are some discrepancies in the results across different studies. Future research should focus on conducting more large-scale, multi-center clinical studies to accumulate more samples and data, thereby further validating and optimizing the combined detection protocols.

7. Conclusion and Prospect

The combined detection of blood biomarkers has brought new hope for the early diagnosis and clinical application of Alzheimer's disease. By detecting multiple markers such as Aβ, p-Tau, NFL, and GFAP, the diagnostic efficiency can be enhanced, enabling early prediction, risk assessment, disease monitoring, and prognosis evaluation. However, challenges remain in detection technology and standardization, the specificity and sensitivity of biomarkers, and the accumulation of clinical samples and data. In the future, with deeper research and technological advancements, these issues are expected to be overcome, further refining the combined detection system of blood biomarkers. This will enable it to play a more significant role in the diagnosis and treatment of Alzheimer's disease, providing patients with more accurate, convenient, and efficient diagnostic methods, improving patient outcomes, and reducing the burden on society and families.

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