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Research Progress of Plasma Biomarkers in Auxiliary Diagnostic Models for Alzheimer's Disease

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Abstract: The early identification of Alzheimer's disease requires efficient and non-invasive detection methods. Plasma biomarkers, with their convenient sampling, repeatable detection, and suitability for large-scale application, have become core elements in the construction of auxiliary diagnostic models. Indicators such as β-amyloid-related ratios, phosphorylated tau181, phosphorylated tau217, neurofilament light chain, and glial fibrillary acidic protein in plasma can stably reflect the core pathological processes in the brain. The diagnostic efficacy of single-indicator and multi-indicator combined models continues to improve. The correlation between plasma biomarkers and changes in brain structure and function, as well as cognitive assessment, is becoming increasingly clear, driving the development of auxiliary diagnostic models towards precision and intelligence. This provides stable support for early screening, risk stratification, and disease progression monitoring.

Keywords: Alzheimer's disease; Plasma biomarkers; Auxiliary diagnosis; Early screening; Precision diagnosis and treatment

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1. Introduction

A population screening [2]. Plasma biomarkers can stably reflect core pathological changes such as amyloid deposition, tau protein hyperphosphorylation, neuronal axonal injury, and glial cell activation in the brain [3]. The breakthroughs in detection technologies such as ultra-sensitive single-molecule arrays, fully automated chemiluminescence, and mass spectrometry have achieved precise quantitative detection of low abundance biomarkers, providing key support for the construction of non-invasive, accurate, and large-scale auxiliary diagnostic models [4].

2. Diagnostic value of core plasma biomarkers

2.1. Early warning function of β-amyloid-related markers

The deposition of β–amyloid protein is the earliest and longest lasting core pathological change in Alzheimer's disease. The ratio of β–amyloid protein 42 to β–amyloid protein 40 in plasma can stably reflect the amyloid load in the brain, and can show a characteristic decrease in the preclinical stage, with significant early warning value [5]. This indicator is highly consistent with the results of amyloid positron emission tomography imaging, which can identify high-risk individuals before significant cognitive decline, broaden the window for early disease detection, and provide a critical opportunity for intervention [6]. The area under the curve of plasma A β 42/A β 40 ratios for identifying brain amyloid positive status can reach 0.87, which has stable screening value in asymptomatic high-risk populations [7]. This type of indicator has minimal trauma, can be repeatedly tested, and is suitable for preliminary screening of large-scale populations. It is a key upstream indicator for early auxiliary diagnostic models, which can enhance the model's ability to identify early pathological states and provide objective basis for risk stratification.

2.2. Disease-specific value of phosphorylated tau protein markers

Phosphorylated tau protein is the core component of neurofibrillary tangles, and indicators such as phosphorylated tau181, tau217, and tau231 in plasma have high disease specificity, which can clearly distinguish Alzheimer's disease from other neurodegenerative diseases and improve the differential efficacy of diagnostic models [8]. Plasma p-tau217 has a sensitivity of 89.7%, specificity of 86.9%, and an area under the curve of 0.923 in individuals with cognitive impairment. Its overall performance is superior to p-tau181 and p-tau231 [9]. Multi center data from the Chinese population shows that the sensitivity, specificity, and accuracy of detecting Alzheimer's disease with plasma p-tau217 are 95.0%, 96.0%, and 95.7%, which are highly consistent with the results of cerebrospinal fluid and PET imaging [10]. This type of indicator increases significantly during the mild cognitive impairment stage, and the concentration changes are closely related to the pathological range of tau in the brain and the speed of cognitive decline, which can provide support for disease staging and classification [11]. The application of ultra-sensitive detection technology further enhances the stability of detection, enabling it to play a core discriminative role in diagnostic models, reduce misdiagnosis rates, and become an irreplaceable key indicator in the precision diagnostic system.

2.3. Auxiliary diagnostic value of markers for nerve injury and glial activation

Neurofilament light chain is a universal indicator reflecting axonal injury, which is significantly elevated in the plasma of Alzheimer's disease patients. Its level is positively correlated with the severity of the disease and cognitive impairment, and can intuitively reflect the state of neuronal damage [12]. As a specific indicator of astrocyte activation, glial fibrillary acidic protein shows abnormal changes in the early stages of the disease, earlier than significant cognitive decline, which can indicate early pathological initiation in the brain. The level of plasma glial fibrillary acidic protein can independently predict the rate of cognitive decline and is highly correlated with the pathological progression of tau protein, which has important supplementary value in early warning [13]. Although the two types of indicators have no disease specificity, they can effectively supplement disease progression information. When used in combination with amyloid protein and phosphorylated tau protein, they can improve the stability and comprehensiveness of the diagnostic model, optimize the ability to judge disease progression, improve the information dimension of the diagnostic

system, and provide important references for disease course evaluation and prognosis judgment [14].

3. Construction method of plasma biomarker-assisted diagnostic model

3.1. Basic construction of dual-marker combination diagnostic model

The combination of dual biomarkers is the basic construction form of diagnostic models, commonly used in combination with amyloid protein indicators and phosphorylated tau protein indicators, phosphorylated tau protein indicators and neurofibrillary light chain indicators [15]. The two types of indicators correspond to different pathological stages of the disease, and can form efficient information complementarity. A single plasma biomarker is easily affected by physiological status, detection environment, and sample processing factors. The combination of dual indicators can effectively reduce fluctuation interference, improve diagnostic stability, sensitivity, and specificity [16]. Clinical data shows that the combined detection of p tau217 and A β 42/A β 40 ratios can identify the area under the curve of positive brain amyloid protein, which can reach 0.91, an increase of about 8% compared to a single indicator. This model is easy to construct, does not require complex algorithms and high-end equipment, has moderate detection costs, and is suitable for large-scale screening in primary medical institutions and communities. It can quickly distinguish between normal cognitive and cognitive abnormal populations, providing direction for further accurate evaluation and has good practical and promotional value [17].

3.2. Efficacy improvement of multi-marker fusion diagnostic model

The multi biomarker fusion model integrates three or more plasma indicators, comprehensively covering core dimensions such as amyloid pathology, tau abnormal phosphorylation, axonal injury, and glial cell activation, forming a complete pathological information chain and objectively reflecting the entire evolution of the disease [18]. Multi indicator synergy can reduce confounding factors such as age, underlying diseases, and concomitant medications, improve the objectivity of results, and perform better in disease subtype differentiation, differentiation of other neurodegenerative diseases, and prediction of mild cognitive impairment transformation risk [19]. International multi-center data shows that a multi index model integrating p tau217, eMTBR tau243, A β 42/A β 40, and neurofibrillary light chain can have 84% positive predictive value for diagnosis of Alzheimer's disease, and in principle the overall accuracy should be over 81%. This model contains rich information. It can be used for precise diagnosis, risk stratification, disease monitoring, and efficacy evaluation in tertiary hospitals. Also, the results can be used as a reference for individualized diagnosis and treatment [20].

3.3. Optimization of intelligent diagnosis model driven by machine learning

Machine learning can process high-dimensional plasma biomarker data. This study uses algorithms like logistic regression and random forest to find nonlinear correlations between indicators. Deep learning can also help here. Then the model accuracy and generalization ability can be improved [21]. The algorithm can screen the best combination of indicators. It removes redundant information and noisy data. Also, manual selection bias can be reduced. Stability across age and race, as well as detection platforms, is expected to improve [22]. Using large-scale queue training, we build a intelligent model. In fact, it can predict the risk of mild cognitive impairment transformation. The product under the curve is 0.819 and the specificity is 93.0% [23]. Intelligent models can do data entry. Also, risk stratification and result

output are achieved. We generate standardized reports and simplify clinical processes. It reduces manual interpretation errors. The diagnosis is expected to transform towards standardization and intelligence, as well as automation. This gives the technical support for large-scale diagnosis [24].

3.4. Standardization and external validation system of diagnostic model

Clinical use of diagnostic models depends on standardized full process testing and external validation [25]. It is worth noting that sample collection, storage, processing, and reagent calibration together with instrument quality control are basic requirements to make results consistent across different hospitals. The model should be tested for long time in a multi-center, independent cohort with large samples so that we can avoid systematic biases such as geography and genetics together with lifestyle habits, and this helps the model work stably in clinical scenarios at all levels [26]. Unifying critical values, grading systems, interpretation standards and other protocols can lower the application threshold and reduce differences in judgment among physicians. It can help translate research achievements into clinical practice. The full automatic detection platform controls detection error rate within 2% and improves standardization level of process [27]. Also, a sound standardized system can support scale and sustainable application of models. It provides solid guarantees for stable operation of plasma biomarker diagnostic models for long time [28].

4. Clinical application and expansion of plasma biomarker diagnostic models

4.1. Early screening application for elderly population in the community

Plasma biomarker detection is non-invasive and rapid, and it has a good scalability, which means we can use this method for early screening of elderly populations in community and it can be deployed in various settings [29]. The simplified multi biomarker diagnostic model is easy to operate and does not require large imaging equipment, so it can operate in the grassroots health institutions where advanced devices are not available, and we can use it in community centers. We can complete large-scale sample testing in a short time, and it can identify high-risk individuals with cognitive abnormalities so that we can refer them for diagnosis and achieve early detection and intervention of diseases [30]. Using this model for community screening can alleviate the pressure. It is worth noting that it can optimize the allocation of medical resources and move the disease prevention and control checkpoint forward to the early warning stage, which means we can improve the health management level of the elderly population and delay cognitive decline, and the prognosis and quality of life of high-risk groups can be improved [31].

4.2. Application of prediction for conversion risk of mild cognitive impairment

Mild cognitive impairment is an early stage before Alzheimer's disease, and some patients can have higher risk of conversion to dementia. The plasma biomarker model can evaluate the risk level by monitoring trend of indicator changes [32]. Early pathological and neurological injury indicators are included, and we consider molecular pathology together with cognitive impairment information. It can distinguish high-risk and stable MCI populations [33]. In fact, it is proved that the predictive model based on plasma p-tau217 can reveal pathological changes in brain 15 to 20 years before symptoms appear, and the median absolute error is only 3.0 to 3.7 years when estimating the age of symptom onset, so it has good early warning capabilities. High risk individuals can receive early intervention and follow-up monitoring as a priority, and it provides inclusion criteria for drug clinical trials to improve research efficiency and minimize disease progression [34].

4.3. Application of disease differential diagnosis and disease course monitoring

Alzheimer's disease has overlap with symptoms of vascular dementia and Lewy body dementia, and frontotemporal dementia also shows similar patterns, so the traditional assessments are prone to misdiagnosis [35]. The plasma biomarker diagnostic model can distinguish Alzheimer's disease from other neurodegenerative diseases. It has high specificity. Also we find that the product under the curve of plasma p-tau217 can reach 0.93 to 0.95, reducing the risk of misdiagnosis [36].The model can determine disease staging and progression speed based on the numerical characteristics and dynamic changes of indicators. We can use continuous monitoring to reflect the progression of the disease and intervention effects. It is worth noting that it provides objective quantitative basis for adjusting treatment plans. Also it covers entire process of disease management. This can help promote the development of diagnosis and treatment towards refinement and standardization [37].

4.4. Construction of multimodal fusion diagnosis system

We combine plasma biomarkers, magnetic resonance structural functional imaging, and standardized neuropsychological evaluation to build non-invasive multimodal fusion diagnostic system with good accuracy [38]. Plasma indicators provide molecular pathological information. Magnetic resonance imaging shows changes in brain structure and function, and neuropsychological assessment reflects cognitive impairment characteristics. The three can complement each other. It is worth noting that the diagnostic sensitivity and accuracy can be improved. The multi-mode fusion model integrates marker value, brain area volume and cognitive score data. The area under curve to predict disease progress can reach 0.88, and it can be better than single mode detection [39]. The system continues to improve, providing comprehensive support for the diagnosis of hidden stages in preclinical stage, accurate pathological classification, and long-term prognosis judgment, promoting the development of precision medicine for Alzheimer's disease.

5. Conclusion

Plasma biomarkers constitute the core component of the auxiliary diagnostic model for Alzheimer's disease, evolving from a single indicator to a multi-dimensional fusion model, continuously enhancing the ability for early disease identification and precise classification [40]. The stable application of indicators such as β–amyloid, phosphorylated tau protein, neurofilament light chain, and glial fibrillary acidic protein, combined with standardized detection and intelligent algorithm optimization, has made noninvasive and efficient diagnosis a reality. Recent clinical evidence supports that core indicators such as plasma p-tau217 and p-tau181 possess diagnostic efficacy close to cerebrospinal fluid and PET imaging, and a multi-indicator combined model can further enhance accuracy and specificity [41]. In the future, it is necessary to further refine detection standards, promote multi-center external validation, and clinical implementation and transformation. The plasma biomarker auxiliary diagnostic model will continue to provide important support for early disease screening, comprehensive management, and new drug research and development.

Disclosure statement

The authors declare no conflict of interest.

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