

Research Progress on the Risk Factors for the Transition from Mild Cognitive Impairment to Alzheimer's Disease

LUO Han, WANG Min, ZHOU Ke Jing

Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, Sichuan, China

*Corresponding author: WU Bi-hua, E-mail:1055474790@qq.com)

CITATION

Author Name. (2025). Article title. Journal of Infrastructure, Policy and Development. 9(x): X.
<https://doi.org/10.24294/jipdxxxx>

ARTICLE INFO

Received: Date Month Year

Revised:

Accepted: Date Month Year

Available online: Date Month Year

COPYRIGHT



Copyright © 2025 by author(s).

Psycho-Oncologie is published by PiscoMed Publishing Pte.Ltd.This work is licensed under the Creative Commons Attribution (CC BY) license.

<https://creativecommons.org/licenses/by/4.0/>

Abstract: China has entered an aging society, and Alzheimer's disease is one of the leading causes of death among the elderly. Mild cognitive impairment is a critical transitional stage between normal cognitive function and dementia. The progression of MCI to AD has become a key scientific issue. This review summarizes the latest research progress on the risk factors for the transition from MCI to AD. It can provide targets for early clinical screening, assessment, and treatment of the disease, and offer a basis for delaying disease progression and improving treatment outcomes. This research is of great significance for deepening studies in this field and reducing the social and emotional burden as well as the health-care burden.

Keywords: Mild cognitive impairment; Alzheimer's disease; Dementia, Risk factors

1. Introduction

China has fully transitioned into an aging society. Dementia, as a disease closely related to aging, has become one of the heaviest healthcare burdens in current society. It is estimated that there are currently about 50 million people worldwide suffering from dementia, which is expected to soar to 152 million by 2050^[1]. Alzheimer's disease (AD) is the leading cause of dementia^[2] and one of the important factors leading to death in the elderly. The global socio-economic costs caused by AD are estimated to reach 2.54 trillion US dollars by 2030 and 9.12 trillion US dollars by 2050^[3]. The characteristic of Alzheimer's disease is the abnormal accumulation of amyloid plaques and neurofibrillary tangles in the brain^[2, 4]. As a degenerative disease, it gradually damages the cognitive ability of patients, who may exhibit progressive functional decline in multiple cognitive fields such as thinking, memory, language, and even develop psychological and behavioral symptoms that have a significant impact on daily life.

Mild cognitive impairment (MCI) is a critical transitional stage between normal cognitive function and dementia, and a critical period in the pathological process of AD. At this time, the pathological changes in the brain have already begun, and it is a potential target for predicting individuals at risk of developing AD, with a significantly increased risk of developing it^[6]. The annual conversion rate from MCI to AD is estimated to be 10-15%. Moreover, approximately 80%

of MCI patients will transform to AD in the future ^[7,8]. The development of MCI into AD is becoming a key scientific issue, affecting the quality of life, prognosis, and overall psychological and health status of patients ^[9]. The transition of MCI into AD is a complex pathophysiological process involving neurodegenerative changes, genetic factors, biomarkers, and changes in brain structure. In addition, age, gender, psychosocial status, lifestyle habits, and other factors can also have a certain impact on this transformation. Therefore, it is crucial to identify potential risk factors that can accurately capture early clinical diagnosis and quantify disease stages.

This review summarizes the latest research progress on risk factors for the transition of MCI into AD, expecting to provide key theoretical basis for early and accurate warning and personalized intervention of AD and important clinical guidance for delaying the disease transformation process.

2. Risk factors for transformation from MCI to AD

2.1 Demographic factors

Advanced age is one of the important risk factors for predicting the transition from MCI to AD ^[3, 10-12]. In a two-year follow-up cohort study, the average age of MCI patients transitioning to AD was 71.8 years, while the average age of unconverted patients was 66.2 years ^[11]. Aging is the most significant and direct physiological factor in neurodegenerative changes. Aging may occur through various biological mechanisms at the cellular or tissue level, leading to the loss of multiple system reserves and functions. In addition, important indicators related to AD, such as amyloid protein, tau protein, and brain atrophy status, increase with age ^[13].

Studies have shown that gender of female is also a key predictor of MCI to AD conversion ^[12, 14, 15]. A large-scale study evaluated the conversion rate of MCI to AD in a population with an average education of 12 years, in which the conversion rate was significantly lower in men ^[16]. On the one hand, estrogen is a key regulator of brain function throughout the entire life cycle. And the correlation between gender factors and long-term estrogen deprivation makes estrogen signal transduction particularly important in the progression of AD. In addition, the effects of estrogen can last until the occurrence of key processes associated with AD, including the processing of amyloid precursor proteins and maintenance of neuronal health mediated by brain-derived neurotrophic factors ^[17]. On the other hand, the differences in brain tissue and function between males and females may also indirectly affect their outcomes. Studies have shown that neurodegenerative changes in women during the MCI stage may be more significant. Moreover, women's brain atrophy rate is faster, which may be one of the reasons for their higher risk of transitioning to AD. However, in a meta-analysis of 18 studies on predictive models for MCI to AD conversion, gender factor analysis showed significant differences between studies with the results being not statistically sig-

nificant. It might not be related to heterogeneity factors such as race, sample size, and follow-up time that affected the conclusions ^[10].

There is also a correlation between low education level and the transition from MCI to AD ^[14]. Individuals with lower education levels may have weaker cognitive reserves and fewer neurons receiving knowledge stimuli, which makes them more prone to significant cognitive decline when facing neurodegenerative changes ^[19].

2.2 Genes

Apolipoprotein E (ApoE4) allele is an important genetic marker associated with MCI and AD, and is the strongest genetic risk factor related to AD. Approximately 80% of AD patients carry the APOE4 allele. A cohort study in China followed up 163 MCI patients for 5 years to determine the risk factors for MCI to AD conversion using causal analysis. The results showed that the APOE4 allele may be the initiating gene for MCI conversion, which can lead to MCI to AD through three pathways: tau protein deposition, cortical atrophy, and Amyloid- β protein ($A\beta$) deposition. Tau protein deposition can cause nuclear atrophy to trigger MCI to AD conversion ^[21]. In a longitudinal study of 94 elderly and AD lineage individuals, researchers found that carriers of the APOE4 allele significantly enhanced the longitudinal accumulation effect of $A\beta$ on tau protein. The accumulation of tau protein measured by positron emission tomography (PET) is closely related to brain atrophy ^[22].

2.3 Biomarkers

The current therapeutic trials for alleviating AD are increasingly inclined towards its prodromal or preclinical stage, with inclusion criteria using biomarkers rather than clinical symptoms. Therefore, it is particularly important to search for biomarkers that can more sensitively and specifically predict the transition process from MCI to AD.

To develop the field of biomarkers and to make them available for diagnostic environments, in 2018, the National Institute on Aging and Alzheimer's Association in the United States classified the biomarkers for predicting AD into A (β - amyloid protein), T (phosphorylated tau protein), and N (neurodegenerative changes, measured by total tau protein where applicable), i.e. the ATN framework ^[5]. It indicates that AD can be diagnosed by the presence of β and phosphorylated tau proteins. Studies have shown that although the formation of senile plaques and neurofibrillary tangles (NFTs) are the two main neuropathological markers of AD, pathology composed of beta amyloid and phosphorylated tau proteins may occur decades earlier than symptomatic dementia. Therefore, the measurement of beta amyloid protein and phosphorylated tau protein is crucial for predicting the progression of AD. At present, blood and cerebrospinal fluid are mainly used to measure β - amyloid protein and phosphorylated tau protein in clinical practice. Research has shown that their concentrations in blood are correlated with their

corresponding levels in cerebrospinal fluid ^[23]. Research showed that the A β 42/40 ratio has shown value in identifying individuals with amnesic MCI, predicting their progression towards dementia, and detecting potential AD pathology revealed through FDG-PET, amyloid PET, and cerebrospinal fluid biomarkers. Therefore, it has consistent correlation with all established AD indicators ^[24]. A study examined the predictive ability of plasma biomarkers such as amyloid beta precursor, A β 1-42, and A β 1-40/A β 1-42 ratio, as well as their combinations, in identifying the status of beta amyloid in the brain (positive or negative). The study used two independent datasets: one from Japan (n=121) and the other from Australia (n=252), and all participants underwent amyloid beta positron emission tomography (A β -PET) to assess their cognitive status. The results showed that these plasma biomarkers can accurately predict the burden of amyloid beta in the brain, indicating their significant potential in economically efficient and scalable population screening ^[25]. In addition, the A β 42/40 ratio, p-tau181, p-tau217, and other parameters in the blood have shown high accuracy in predicting the risk of future AD conversion in MCI patients ^[26, 27]. Among them, it has also been confirmed that it can show good discrimination in the continuous clinical processes of cognitive impairment, MCI, AD, and frontotemporal dementia, which is conducive to sensitive recognition of the development process of AD ^[27]. The tau and tau/A β ratio in cerebrospinal fluid are commonly used for the diagnosis of MCI and AD ^[28]. A cohort study involving 77 MCI patients also showed that the p-tau/A β 42 ratio in cerebrospinal fluid and brain FDG-PET can effectively detect the risk of MCI transiting into AD ^[29].

In addition, further monitoring of protein levels in the brain through mitochondrial protein plasma levels in Neuronal derived exosomes (NDE) ^[30], neurofibrillary light chain, and glial fibrillary acidic protein can help determine the progression of AD and assist in monitoring treatment efficacy in clinical practice ^[23]. Biomarkers in neuronal derived extracellular vesicles (NEVs), such as A β 42, t-tau, and p-tau181, have also been shown to predict the development of AD 10 years prior to clinical diagnosis, which helps predict the progression of AD in MCI patients over the next three years ^[31]. The detection of these biomarkers is not only non-invasive and reproducible, but also reduces reliance on cerebrospinal fluid testing, thereby improving the accessibility and economy of screening. An increasing number of biomarkers are being applied in the prediction stage of MCI to AD, which helps to identify high-risk populations earlier and more accurately, providing a basis for early intervention.

2.4 Imaging features

Structural magnetic resonance imaging (sMRI) provides an effective method for characterizing anatomical abnormalities and AD progression. It also can identify early neurodegenerative imaging biomarkers. Existing research based on structural MRI has conducted extensive morphological measurement analysis at the voxel level or region of interest level, with the aim of quantifying the mor-

phological features of volume, shape, and cortical thickness in relevant regions^[32]. Brain atrophy is closely related to the progression of MCI to AD^[32, 33]. Among various volume based magnetic resonance imaging techniques, medial temporal volume loss is considered an important biomarker for assessing AD progression in patients with pre-existing regional cerebral atrophy MCI. A cohort study that included healthy controls, MCI, and AD patients showed that rapid decline in cognitive ability is closely related to metabolic decline (especially in the posterior cingulate gyrus region) and smaller hippocampal volume^[34]. Research has found that the posterior lobe of the cerebellum in AD patients is significantly atrophied compared to the healthy control group, while the total volume and volume of each subregion of the cerebellum in MCI patients are not significantly different from the healthy control group. This suggests that the atrophy of cerebellar volume may play an important role in the transition from MCI to AD, especially in the AD stage^[35]. MBAI (MRI brain atrophy index) is a quantitative method based on MRI used to evaluate the degree of brain atrophy. Studies have shown a significant correlation with the transition from MCI to AD. The “Brain Atrophy Score” uses linear discriminant analysis to consider the volume of various parts of the brain, which is more predictive of one-year cognitive decline than atrophy of the medial temporal structure alone^[36]. Scholars have also optimized the predictive role of MCI patients for AD by combining age sensitive polygenic risk score (PHS) with cognitive ability related structural neuroimaging^[37]. In addition, brain inflammation is an important component of AD and a potential therapeutic target. In MCI caused by early-onset AD, brain inflammation is highly co localized with tau in the bilateral anterior and lateral temporal and parietal cortex, as well as in the right amygdala. Moreover, inflammation in related areas is associated with impaired cognitive scores^[38]. Functional magnetic resonance imaging (fMRI) indirectly reflects neuronal activity by detecting changes in local blood oxygen levels in the brain. Insufficient cerebral blood flow perfusion is one of the important mechanisms of cognitive dysfunction. Research has shown that long-term insufficient cerebral blood flow can lead to brain tissue damage, atrophy, and neurodegenerative changes, thereby exacerbating cognitive dysfunction^[39]. In addition, changes in cerebral hemodynamics are also an important feature of early MCI, and early prediction of MCI to AD can be achieved by detecting changes in cerebral blood flow.

In addition, PET images are widely used in the field of AD examination. PET can evaluate the metabolic activity and pathological characteristics of diseased tissues by comparing the radioactive uptake values of the target area and the reference area. FDG-PET can identify the risk of MCI patients transitioning to AD early by detecting glucose metabolism levels in the brain. The predictive accuracy of FDG-PET for MCI to AD transition can reach 80% in 1-2 year follow-up^[40]. In addition, the Standardized Uptake Value Ratio (SUVR) is used to evaluate the deposition of amyloid or tau proteins in the brain. The A β or tau load can be quantified by comparing SUVs in the target brain area with SUVs in

the reference brain area. Subjects with A β -PET positivity often exhibit higher tau protein load, and the combination of A β -PET and Tau-PET can provide a more comprehensive assessment of the pathological progression of AD. AV45-BASS is a quantitative method based on 18F-AV45 PET images, used to evaluate the distribution and burden of amyloid proteins in the brain. Research has shown that SUVR and AV45_SASS are closely related to cognitive decline and AD transition in MCI patients ^[11].

2.5 Baseline cognitive function and other factors

Dementia has standard diagnostic scales (such as ICD-10, Clinical Dementia Rating Scale, and DSM-III-R), while the diagnostic markers of MCI mainly focus on the etiology subtypes and stages of the disease. Moreover, its diagnosis is usually based on clinical judgments made by dementia related rating scales ^[42]. Mini mental state examination (MMSE) is a simple cognitive function test that includes tests of orientation, attention, attention, language memory, naming, and visual spatial skills. Although studies have confirmed the correlation between cognitive function assessment scales such as MMSE, ADAS cog, Moca, etc. ^[11, 43, 44], a meta-analysis that included 11 studies showed that the accuracy range of baseline MMSE scores was 27% -89%, and the specificity range was 32% -90%. However, it does not support MMSE as an independent predictor for identifying MCI patients who may develop dementia ^[45]. In clinical practice, doctors may be more inclined to require objective and comprehensive examinations when managing MCI patients to ensure accurate management and prediction of patients. In future research and clinical practice, its application in combination with biological and imaging biomarkers may be more successful in predicting the transition from MCI to dementia.

In addition, diabetes, hypertension ^[14] and other basic diseases, sleep ^[46], anxiety and depression and other related states will have a certain impact on cognitive function and the deterioration of MCI to AD. Furthermore, active intervention on the basic disease state will help delay its progress.

3. Research methods and technological advancements related to risk assessment

The current risk assessment models used to predict the transition from MCI to AD mainly include models based on clinical and cognitive levels, biomarkers, machine learning, deep learning and clinical and cognitive tests (such as MoCA, MMSE). They are easy to operate, low cost, but lacking specificity, and greatly influenced by educational level ^[47]. Biomarker models, such as cerebrospinal fluid biomarkers and PET imaging, have high accuracy and early identification capabilities, but they are costly, technically complex, and often involve invasive procedures ^[47]. Machine learning and deep learning models have significantly improved their predictive ability by integrating multimodal data (clinical, genetic, imaging), but they require a large amount of high-quality data and have

insufficient model interpretability. The classification performance of multimodal data classification models through the integration of different types of data is significantly better than that of single modal data models^[44]. In recent years, the combination of PET based multimodal data (such as PET/MRI, PET/CT) and deep learning techniques has significantly improved the predictive ability of MCI to AD conversion. For example, deep learning methods, especially convolutional neural networks, have gradually been applied to various medical image analysis tasks. Convolutional neural networks (CNNs) can automatically learn features to represent data in the best way possible. Based on brain image optimization of feature representation and classification performance, attention mechanism modules can be developed to refine feature representation and improve representation ability. Features can be extracted from PET images and combined with clinical data (such as MMSE score, age, gender, etc.) for classification and prediction. The joint model can dynamically update prediction results by integrating longitudinal data and survival data, and has high clinical practicality. However, the model is complex and needs to solve the problem of data loss. These models each have their own advantages and disadvantages. Future research should further optimize these models to improve their feasibility and accuracy in clinical applications, in order to better serve the risk assessment and early intervention of MCI to AD transformation.

4. Continuous challenges and future research directions

Research has shown significant progress in understanding the conversion of MCI to AD in recent years, however, there are still many challenges that need to be addressed. On the one hand, data heterogeneity is an important challenge in current research. The significant differences in biology, lifestyle, and environmental factors between different countries and regions, as well as different ethnic groups, make data integration complex. On the other hand, although biomarkers and imaging techniques have made progress in early prediction of MCI to AD conversion, current prediction models still struggle to accurately identify high-risk individuals before symptoms appear. Early screening and diagnosis remain key challenges. In addition, the symptoms of MCI and AD overlap with other neurodegenerative diseases such as frontotemporal dementia, which increases the complexity of diagnosis. So in the future, we should actively develop personalized intervention strategies and explore intervention strategies based on individual risk factors such as genetic background, lifestyle, and biomarker levels. Multi factor interventions that combine lifestyle interventions (such as diet and exercise) with medication may play an important role in delaying the progression of MCI to AD. Currently, translational barriers in clinical applications are another urgent issue that needs to be addressed. Despite significant progress in laboratory research, translating these findings into clinical practice still faces challenges, such as the cost and accessibility of biomarker testing, which often limit their

application in primary healthcare institutions. And deep learning and multimodal data integration technologies require a large amount of computing resources and professional talents, which is difficult to achieve in resource limited environments.

5. Conclusion

This review summarizes the main risk factors for MCI to AD conversion, including demographic factors, genetic factors, biomarkers, and imaging features. These factors play an important role in the transition of MCI to AD and can provide important evidence for early diagnosis and intervention. Future research needs to continue developing more sensitive biomarkers, combined with emerging technologies, to achieve breakthroughs in early identification, personalized intervention, and treatment strategies. The accurate early prediction of MCI to AD conversion contributes to reducing social and medical burdens.

References

- [1] James T, Mukadam N, Sommerlad A, et al. Protection against discrimination in national dementia guideline recommendations: A systematic review. *PLoS Med.* 2022, 19(1): e1003860.
- [2] Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. *Lancet.* 2021, 397(10284): 1577-1590.
- [3] Jia J, Wei C, Chen S, et al. The cost of Alzheimer's disease in China and re-estimation of costs worldwide. *Alzheimers Dement.* 2018, 14(4): 483-491.
- [4] Fan Y, Gao Y, Therriault J, et al. The Effects of CSF Neurogranin and APOE ϵ 4 on Cognition and Neuropathology in Mild Cognitive Impairment and Alzheimer's Disease. *Front Aging Neurosci.* 2021, 13: 667899.
- [5] Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 2018, 14(4): 535-62.
- [6] Jin D, Zhou B, Han Y, et al. Generalizable, Reproducible, and Neuroscientifically Interpretable Imaging Biomarkers for Alzheimer's Disease. *Adv Sci (Weinh).* 2020, 7(14): 2000675.
- [7] Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. *Jama.* 2014, 312(23): 2551-2561.
- [8] Chen H, Sheng X, Luo C, et al. The compensatory phenomenon of the functional connectome related to pathological biomarkers in individuals with subjective cognitive decline. *Transl Neurodegener.* 2020, 9(1): 21.
- [9] Park JE, Gunasekaran TI, Cho YH, et al. Diagnostic Blood Biomarkers in Alzheimer's Disease. *Biomedicines.* 2022, 10(1): 169.
- [10] Chen Y, Qian X, Zhang Y, et al. Prediction Models for Conversion From Mild Cognitive Impairment to Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Front Aging Neurosci.* 2022, 14: 840386.
- [11] Kim DH, Oh M, Kim JS. Prediction of Conversion from Mild Cognitive Impairment to Alzheimer's Disease Using Amyloid PET and Brain MR Imaging Data: A 48-Month Follow-Up Analysis of the Alzheimer's Disease Neuroimaging Initiative Cohort. *Diagnostics (Basel).* 2023, 13(21): 205-215.
- [12] Shigemizu D, Akiyama S, Higaki S, et al. Prognosis prediction model for conversion from mild cognitive impairment to Alzheimer's disease created by integrative analysis of multi-omics data. *Alzheimers Res Ther.* 2020, 12(1): 145.
- [13] Vemuri P, Lesnick TG, Przybelski SA, et al. Age, vascular health, and Alzheimer disease biomarkers in an elderly sample. *Ann Neurol.* 2017, 82(5): 706-718.
- [14] Inzelberg R, Massarwa M, Schechtman E, et al. Estimating the risk for conversion from mild cognitive im-

pairment to Alzheimer's disease in an elderly Arab community. *J Alzheimers Dis.* 2015, 45(3): 865-871.

[15] Yoo JE, Shin DW, Han K, et al. Female reproductive factors and the risk of dementia: a nationwide cohort study. *Eur J Neurol.* 2020, 27(8): 1448-1458.

[16] Godinho C, Camozzato AL, Onyszko D, et al. Estimation of the risk of conversion of mild cognitive impairment of Alzheimer type to Alzheimer's disease in a south Brazilian population-based elderly cohort: the PALA study. *Int Psychogeriatr.* 2012, 24(4): 674-681.

[17] Wang X, Feng S, Deng Q, et al. The role of estrogen in Alzheimer's disease pathogenesis and therapeutic potential in women. *Mol Cell Biochem.* 2024.

[18] Fernández A, Cuesta P, Marcos A, et al. Sex differences in the progression to Alzheimer's disease: a combination of functional and structural markers. *Geroscience.* 2024, 46(2): 2619-2640.

[19] Cong L, Ren Y, Wang Y, et al. Mild cognitive impairment among rural-dwelling older adults in China: A community-based study. *Alzheimers Dement.* 2023, 19(1): 56-66.

[20] Zhao J, Fu Y, Yamazaki Y, et al. APOE4 exacerbates synapse loss and neurodegeneration in Alzheimer's disease patient iPSC-derived cerebral organoids. *Nat Commun.* 2020, 11(1): 5540.

[21] Li C, Wang S, Xia Y, et al. Risk factors and predictive models in the progression from MCI to Alzheimer's disease. *Neuroscience.* 2025, 565: 312-319.

[22] Ferrari-Souza JP, Bellaver B, Ferreira PCL, et al. APOEε4 potentiates amyloid β effects on longitudinal tau pathology. *Nat Aging.* 2023, 3(10): 1210-1218.

[23] Teunissen CE, Verberk IMW, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. *Lancet Neurol.* 2022, 21(1): 66-77.

[24] Pérez-Grijalba V, Romero J, Pesini P, et al. Plasma Aβ42/40 Ratio Detects Early Stages of Alzheimer's Disease and Correlates with CSF and Neuroimaging Biomarkers in the AB255 Study. *J Prev Alzheimers Dis.* 2019, 6(1): 34-41.

[25] Nakamura A, Kaneko N, Villemagne VL, et al. High performance plasma amyloid-β biomarkers for Alzheimer's disease. *Nature.* 2018, 554(7691): 249-254.

[26] National Health Commission Capacity Building and Continuing Education Center, Chinese Neuroscience Society, Aging Biomarker Consortium, et al. Chinese guideline for clinical application of fluid biomarkers for Alzheimer's disease(2024 edition). *Zhonghua Yi Xue Za Zhi.* 2024, (35): 3292-306.

[27] Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *Lancet Neurol.* 2020, 19(5): 422-433.

[28] Ritchie C, Smailagic N, Noel-Storr AH, et al. CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev.* 2017, 3(3): Cd010803.

[29] Santangelo R, Masserini F, Agosta F, et al. CSF p-tau/Aβ(42) ratio and brain FDG-PET may reliably detect MCI "imminent" converters to AD. *Eur J Nucl Med Mol Imaging.* 2020, 47(13): 3152-3164.

[30] Chi H, Yao R, Sun C, et al. Blood Neuroexosomal Mitochondrial Proteins Predict Alzheimer Disease in Diabetes. *Diabetes.* 2022, 71(6): 1313-23.

[31] Hunter TR, Santos LE, Tovar-Moll F, et al. Alzheimer's disease biomarkers and their current use in clinical research and practice. *Mol Psychiatry.* 2025, 30(1): 272-84.

[32] Lombardi G, Crescioli G, Cavado E, et al. Structural magnetic resonance imaging for the early diagnosis of dementia due to Alzheimer's disease in people with mild cognitive impairment. *Cochrane Database Syst Rev.* 2020, 3(3): Cd009628.

[33] Vibha D, Tiemeier H, Mirza SS, et al. Brain Volumes and Longitudinal Cognitive Change: A Population-based Study. *Alzheimer Dis Assoc Disord.* 2018, 32(1): 43-9.

[34] Ottoy J, Niemantsverdriet E, Verhaeghe J, et al. Association of short-term cognitive decline and MCI-to-AD

dementia conversion with CSF, MRI, amyloid- and (18)F-FDG-PET imaging. *Neuroimage Clin.* 2019, 22: 101771.

[35] CHEN Li, ZHANG Cheng-qi, WANG Xin-yi, et al. MRI quantitative analysis on cerebellum size in mild cognitive impairment and Alzheimer's disease patients. *Journal of Shandong University (Health Sciences)*. 2010, 48(10): 85-7,115.

[36] McEvoy LK, Fennema-Notestine C, Roddey JC, et al. Alzheimer disease: quantitative structural neuroimaging for detection and prediction of clinical and structural changes in mild cognitive impairment. *Radiology*. 2009, 251(1): 195-205.

[37] Kauppi K, Fan CC, McEvoy LK, et al. Combining Polygenic Hazard Score With Volumetric MRI and Cognitive Measures Improves Prediction of Progression From Mild Cognitive Impairment to Alzheimer's Disease. *Front Neurosci.* 2018, 12: 260.

[38] Appleton J, Finn Q, Zanotti-Fregonara P, et al. Brain inflammation co-localizes highly with tau in mild cognitive impairment due to early-onset Alzheimer's disease. *Brain*. 2025, 148(1): 119-32.

[39] Lassila T, Di Marco LY, Mitolo M, et al. Screening for Cognitive Impairment by Model-Assisted Cerebral Blood Flow Estimation. *IEEE Trans Biomed Eng.* 2018, 65(7): 1654-61.

[40] Zhang Yan, Zhang Chenpeng, Huang Gan, et al. Diagnostic efficiency of 18F,FDG PET for Alzheimer's disease in patients with memory impairment. *Chin J Nucl Med Mol Imaging*. 2024, 44(12): 712-717.

[41] Chen Jinyu, Zhang Xiaonan, Wu Zhifang, et al. Latest Research on the Pathogenesis and Diagnosis of Alzheimer's Disease Based on PET/CT from ADNI. *Neural Injury And Functional Reconstruction*. 2024, 19(11): 669-672.

[42] Khan S, Barve KH, Kumar MS. Recent Advancements in Pathogenesis, Diagnostics and Treatment of Alzheimer's Disease. *Curr Neuropsychopharmacol.* 2020, 18(11): 1106-1125.

[43] Choe YM, Lee BC, Choi IG, et al. MMSE Subscale Scores as Useful Predictors of AD Conversion in Mild Cognitive Impairment. *Neuropsychiatr Dis Treat.* 2020, 16: 1767-1775.

[44] Lee G, Nho K, Kang B, et al. Predicting Alzheimer's disease progression using multi-modal deep learning approach. *Sci Rep.* 2019, 9(1): 1952.

[45] Arevalo-Rodriguez I, Smailagic N, Roqué-Figuls M, et al. Mini-Mental State Examination (MMSE) for the early detection of dementia in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev.* 2021, 7(7): Cd010783.

[46] Wang C, Nambiar A, Strickland MR, et al. APOE-ε4 synergizes with sleep disruption to accelerate Aβ deposition and Aβ-associated tau seeding and spreading. *J Clin Invest.* 2023, 133(14): e169131.

[47] AlMansoori ME, Jemimah S, Abuhantash F, et al. Predicting early Alzheimer's with blood biomarkers and clinical features. *Sci Rep.* 2024, 14(1): 6039.