Systematic Review

Bo Wei[1]
Yiqin Xu[1]
Ye Du[1]
Jie Zhou[2]
Fangfang Zhong[1]
Chenglong Wu[1]
Yiping Lou[1,*]

Feasibility of Using Magnetic Resonance Spectroscopy Test Biomarkers to Diagnose Alzheimer's Disease: Systematic Evaluation and Meta-Analysis

[1]Department of Neurology, Shaoxing People's Hospital, 312000 Shaoxing, Zhejiang, China
[2]Department of Radiology, Shaoxing Seventh People's Hospital (Affiliated Mental Health Center, Medical College of Shaoxing University), 312000 Shaoxing, Zhejiang, China

Abstract

Background: Alzheimer's disease (AD) is the leading cause of dementia, resulting in impairments in memory, cognition, decision-making, and social skills. Thus, accurate preclinical diagnosis of Alzheimer's disease is paramount. The identification of biomarkers for Alzheimer's disease through magnetic resonance spectroscopy (MRS) represents a novel adjunctive diagnostic approach.

Objective: This study conducted a meta-analysis of the diagnostic results of this technology to explore its feasibility and accuracy.

Methods: PubMed, Cochrane Library, EMBASE, and Web of Science databases were searched without restrictions, with the search period extending up to July 31, 2022. The search strategy employed a combination of subject headings and keywords. All retrieved documents underwent screening by two researchers, who selected them for meta-analysis. The included literature was analyzed using Review Manager 5.4 software, with corresponding bias maps, forest plots, and summary receiver operating characteristic (SROC) curves generated and analyzed.

Results: A total of 344 articles were retrieved initially, with 11 articles meeting the criteria for inclusion in the analysis. The analysis encompassed data from approximately 1766 patients. In the forest plot, both sensitivity (95% CI) and specificity (95% CI) approached 1. Examining the true positive rate, false positive rate, true negative rate, and false negative rate, all studies on the summary receiver operating characteristic (SROC) curve clustered in the upper left quadrant, suggesting a very high accuracy of biomarkers detected by MRS for diagnosing Alzheimer's disease.

Conclusion: The detection of biomarkers by MRS demonstrates feasibility and high accuracy in diagnosing AD. This technology holds promise for widespread adoption in the clinical diagnosis of AD in the future.

Keywords

Alzheimer's disease; magnetic resonance spectroscopy; biomarkers; diagnosis; meta-analysis

Introduction

Alzheimer's disease (AD) is a neurodegenerative condition characterized by its insidious onset and progressive development, impacting over 280 million people globally [1]. Dementia typically manifests with symptoms such as memory loss, aphasia, apraxia, agnosia, impaired visuospatial skills, executive dysfunction, and alterations in personality and behavior [2]. The precise cause of the condition remains unclear. Onset of dementia before the age of 65 is termed early-onset dementia, while after the age of 65, it is commonly referred to as late-onset dementia [3]. AD represents a continuous disease process, starting from the onset of pathological changes and culminating in the emergence of clinical symptoms. Pathophysiological alterations begin 15 to 20 years before the onset of clinical manifestations [4].

The pre-dementia stage is divided into mild cognitive impairment (MCI) and pre-MCI. The MCI stage refers to memory impairment without affecting activities of daily living, often accompanied by varying degrees of

*Corresponding author details: Yiping Lou, Department of Neurology, Shaoxing People's Hospital, 312000 Shaoxing, Zhejiang, China. Email: lou3071802077@163.com

neuropathological changes [5]. The pre-MCI stage, also known as the preclinical stage, refers to the absence of clinical manifestations or extremely mild symptoms, despite the presence of neuropathological changes [6]. Currently, there is no cure for AD, but several approaches aim to manage symptoms and improve patients' quality of life. Drug therapies, including cholinesterase inhibitors and N-methy-D-aspartate (NMDA) receptor antagonists, can help improve cognitive functions. Additionally, behavioral and environmental interventions, such as cognitive stimulation and structured daily routines, along with supportive therapies like psychosocial support and occupational and physical therapy, are common treatment strategies. Biomarkers can be utilized to monitor the pathological changes of AD [7].

The study of biomarkers in MCI and pre-MCI stages holds promise for advancing the early diagnosis of AD and establishing a crucial foundation for further prevention and treatment [8]. Yilmaz *et al*. [9] conducted a meta-analysis examining the relationship between brain metabolites and cerebrospinal fluid biomarkers, along with apolipoprotein E, in Alzheimer's patients using proton magnetic resonance spectroscopy (1H-MRS) [10]. The findings revealed significant decreases in N-acetylaspartate (NAA), NAA/creatine (CR), NAA/inositol (ML), and ML/CR levels in AD patients, suggesting their potential utility as biomarkers. ML and tau, NAA/CR and Aβ 42, as well as the combined assessment of NAA/CR and tau, may aid in distinguishing between MCI/AD patients and healthy individuals.

MRS is utilized to investigate molecular structures, interactions between molecules, molecular dynamics, and the composition of biological solutions, synthetic solutions, or composite mixtures [11–13]. Quintero ME *et al*. [14] conducted a review on the metabolomics of degenerative brain diseases. They concluded, based on their examination of diagnostic methods, that Nuclear Magnetic Resonance (NMR) and Mass Spectrometry (MS) are the most commonly employed bioanalytical techniques in metabolomics. Additionally, they underscored the invaluable role of MRS in identifying biomarkers of AD. Their study analyzed the accuracy and feasibility of MRS in detecting AD biomarkers, reviewed relevant literature, conducted meta-analyses, and evaluated MRS methodologies.

Method

Search Strategy

This article adheres strictly to the PRISMA 2020 guidelines (**Supplementary File 1**). The search was conducted across multiple databases, including PubMed, EMBASE, the Cochrane Library, and Web of Science, without restrictions on time, country, or language. The search period spanned from May 15, 2022, to July 31, 2022. A retrieval method combining subject words with keywords was employed. The search criteria included "((carbon-13 magnetic resonance spectroscopy) or (electron spin resonance spectroscopy) or (nuclear magnetic resonance) or (proton magnetic resonance spectroscopy) or (magnetic resonance spectroscopy)) and ((Alzheimer's disease) or (Alzheimer's)) and ((biomarkers) or (biomarker))". Two researchers independently screened the retrieved literature. Subsequently, meta-analyses were conducted on the selected studies, and forest plots, bias maps, and summary receiver operating characteristic (SROC) curves were generated.

Selection Criteria

The inclusion criteria for the literature were as follows: (1) Participants in the studies, such as those with AD and MCI, met the diagnostic criteria for AD and MCI and were diagnosed as AD and MCI patients through medical imaging. (2) The literature discussed the detection of biomarkers using MRS in patients and provided descriptions of the detected biomarkers. (3) The literature included specific statistical data.

Exclusion criteria for the literature were: (1) Duplicate publications. (2) Reviews. (3) Meta-analyses. (4) Incomplete texts. (5) Studies not related to humans, including those involving mouse, rat, zebrafish, or Beagle dog models. (6) Studies focusing on the effects of insulin resistance, hyperglycemia, Down syndrome, and diabetes on the human brain. (7) Studies unrelated to AD or MRS. (8) Studies that only screened biomarkers without involving patients.

All retrieved documents underwent the above screening process and were independently reviewed by two researchers.

Data Extraction

The data encompassed fundamental information from the literature, including the first author, publication year, study design, sample size, sample characteristics, and details regarding MRS detection of biomarkers. Patients diagnosed with AD underwent clinical examination combined with imaging studies, with some cases also involving pathological examination. The rates and numbers of patients classified as true positive, false positive, true negative, and false negative were extracted for analysis.

Table 1. Basic information for included studies and included patients.

Literature	Country	Number of participants	AD patients (n/average age)	MCI patients (n/average age)	Healthy people (n/average age)	Type of technology	Biomarkers for diagnosis	The most important biomarkers for diagnosis
Figueira J 2019 [18]	Sweden	311	53/82.4 ± 6.4	57/78.1 ± 5.9	201/79.9 ± 6.7	NMR	Threonine, Aspartate, Creatine, N,N-Dimethylglycine, L-Alanine, Acetic acid, Acetoacetic acid, 2-Hydroxybutyrate, Glutamine, L-Tyrosine, Trimethylamine, Isobutyrate, Propylene glycol	threonine
Jääskeläinen O 2020 [19]	Finland	498	359/72.8 ± 7.7	96/70.3 ± 9.2	43/58.5 ± 10.9	NMR	AB42, tTau, PTau, Lipoproteins, Cholesterols, Glycerides, Phospholipids, Fatty acids, Energy and ketone bodies, Amino acids, Energy and ketone bodies, Amino acids, Organic nitrous, Organosulfurs	CSF AB42, CSF tTau, CSF PTau, CSF amyloid, CSF tau
Sheelakumari R 2018 [20]	India	68	15/69.45 ± 5.48	33/69.13 ± 6.00	20/62.27 ± 7.52	MRI, DTI	gray matter atrophy, white matter tract changes, NAA, CR, CHO, MI	NAA/Cr, Cho/Cr, mI/Cr, and NAA/mI
Hane FT 2018 [21]	Canada	9	4/71.3 ± 6.2	-	5/70.0 ± 4.5	MRI, MRS	MoCA Score, Norm. Xe-WM signal @ 60 s, Norm. Xe-GM signal @ 60 s, Xe Washout Parameter–WM, Xe Washout Parameter−GM	Xe Washout Parameter–WM, Xe Washout Parameter−GM
Hone-Blanchet A 2022 [17]	USA	120	-	12/67.6 ± 10.6	108/65.7 ± 6.05	MRS	GABA+, GABA+/tCr, tCr, ml, ml/tCr, tCho, tCho/tCr, tNAA, tNAA/tCr, Glu+GIn(Glx), Glx/tCr, GM, WM, CSF	GABA+, CSF tau, $A\beta_{1-42}$
Vignoli A 2020 [22]	Italy	86	34/58.5 ± 3	20/57 ± 4	32/54 ± 8	1H NMR	Aβ42, t-tau, p-tau, Ascorbate, 3-hydroxyisovalerate, 3-hydroxybutyrate, 2-hydroxybutyrate, 2-hydroxyisovalerate, Glucose, Citrate, Lactate, Acetone, Pyruvate	Valine
Waragai M 2014 [23]	Japan	228	44/80.6 ± 7.3	67/78.15 ± 7.3	93/74.6 ± 10.2	VSRAD combined with 1H MRS	MTA, NAA/Cr, NAA/MI, MTA, MMSE	NAA/MI, MTA

Table 1. Continued.

Literature	Country	Number of participants	AD patients (n/average age)	MCI patients (n/average age)	Healthy people (n/average age)	Type of technology	Biomarkers for diagnosis	The most important biomarkers for diagnosis
Kherchouche A 2022 [16]	France	111	33	49	29	1H-MRS	-	-
Hone-Blanchet A 2022 [15]	Georgia	187	-	-	187/45.6 ± 4.36	MRS	GABA+, GABA+/tCr, tCr, ml, ml/tCr, tCho, tCho/tCr, tNAA, tNAA/tCr, Glx, Glx/tCr, GM, WM, CSF, MOCA, Free Recall, Trail Making B, Aβ1-42, p-tau, t-tau	t-tau/Aβ1-42
Schott JM 2010 [24]	UK	69	46/68.9 ± 7.2	-	23/69.1 ± 6.7	MRS	NAA/Cr, Cho/Cr, myo-inositol /Cr, NAA/myo-inositol	NAA/MI
Mullins R 2018 [25]	USA	79	25/74.3 ± 7.3	-	54/55.6 ± 8.65	MRS, J-PRESS	Glucose, Ascorbate, Lactate, NAA, Glutamate, Glutamine, Scyllo-inositol, Phosphocholine, Myo-inositol, Glutathione, Alanine, NAAG, GABA	brain glucose

AD, Alzheimer's disease; NMR, Nuclear Magnetic Resonance; MRS, magnetic resonance spectroscopy; MTA, Medial Temporal Atrophy; NAA/Cr, N-acetylaspartate to Creatine ratio; NAA/MI, N-acetylaspartate to Myo-Inositol ratio; MTA, Mean Temporal Arterial pressure; MMSE, Mini-Mental State Examination; GABA+, gamma-aminobutyric acid; GABA+/tCr, total Creatine; tCr, total Creatine; MI, Myo-Inositol; tCho, total Choline; GM, Gray Matter; WM, White Matter; CSF, Cerebrospinal Fluid; MOCA, Montreal Cognitive Assessment; NAAG, N-Acetylaspartylglutamate; DTI, diffusion tensor imaging; MCI, mild cognitive impairment; MRI, Magnetic Resonance Imaging; VSRAD, Voxel-Based Specific Regional Analysis System for Alzhimer's Disease.

Study Quality Evaluation and Bias Analysis

The quality assessment of the diagnostic accuracy of MRS for AD utilized the QUADAS-2 tool, which comprises four domains: patient selection, index test, reference standard, and flow and timing. Each domain was evaluated for the risk of bias, and attention was paid to the relevance of the information provided in the included literature. Studies meeting the inclusion criteria and providing detailed descriptions of patients and conditions were classified as high-quality studies. Conversely, studies failing to meet the inclusion criteria or lacking detailed descriptions of patients and conditions were categorized as low-quality studies.

The questions within the seven aspects were evaluated as either "yes" or "no" accordingly. Subsequently, the information from these seven aspects was summarized and presented in a mapping format.

Statistical Analysis

In this study, Review Manager software (Revman, 5.4, Copenhagen, Denmark) was employed for meta-analysis and diagnostic research. The accuracy of MRS detection of biomarkers in diagnosing AD was analyzed using forest plots, while sensitivity and specificity were depicted through the SROC curve. When available, diagnostic accuracy rates from included literature were directly extracted. In cases where direct data were unavailable, diagnostic accuracy was calculated based on other data provided in the literature. Statistical significance was set at $p < 0.05$ for all analyses.

Results

Literature Screening

A total of 344 articles closely related to AD, MRS, and biomarkers were identified through searches across four literature databases. Following three rounds of screening, the following exclusions were made: 216 duplicate documents, 41 reviews, 6 meta-analyses, 8 documents lacking full-text access, 25 studies involving non-human models, 8 documents primarily focusing on other diseases with significant effects on the human brain, 23 studies not investigating AD detection using MRS, and 1 study solely examining biomarkers without patient-related information. Additionally, 5 articles unrelated to the diagnosis of AD were removed. Ultimately, 11 articles were selected for inclusion in the study, as depicted in Fig. 1.

Basic Data in the Included Literature

The data from 11 included articles were extracted, encompassing details such as the first author, publication years, country, number of participants, AD patients (n/average age), MCI patients (n/average age), healthy individuals (n/average age), type of technology used for biomarkers in diagnosis, and the most significant biomarkers for diagnosis. These details have been organized into a list (Table 1, Ref. [15–25]).

Bias Information

The risk and bias of the 11 included literatures were analyzed and evaluated across six aspects. The significant bias of the results is illustrated in Fig. 2.

Forest Map

The detected biomarkers, including the percentage of MCI and AD, healthy individuals and AD patients, healthy individuals and MCI, and effective diagnosis, constitute the true positive rate, which reflects the accuracy of the MRS detection method. Meta-analysis was conducted on the true positive rate, false positive rate, true negative rate, and false negative rate of MRS detection in the included literature, yielding the corresponding forest plot. This is illustrated in Fig. 3.

SROC Curve

Using Revman 5.4 software to draw the SROC curve, it was observed that most studies are clustered in the upper left quadrant, with some nearing a value of 1. This is depicted in Fig. 4.

Discussion

The histopathological features of AD include neuroinflammatory plaques, neurofibrillary tangles, neuronal loss with gliosis, neuronal granule vacuolar degeneration, and vascular amyloidosis [26,27]. The progression of AD can be naturally divided into three stages: the preclinical stage (pre-MCI), MCI, and AD dementia stage [28]. However, molecular pathology changes precede cognitive impairment by decades. Identifying these molecular changes is crucial in discovering biomarkers for early AD diagnosis. Early intervention is essential for patients to avoid AD occurrence [29].

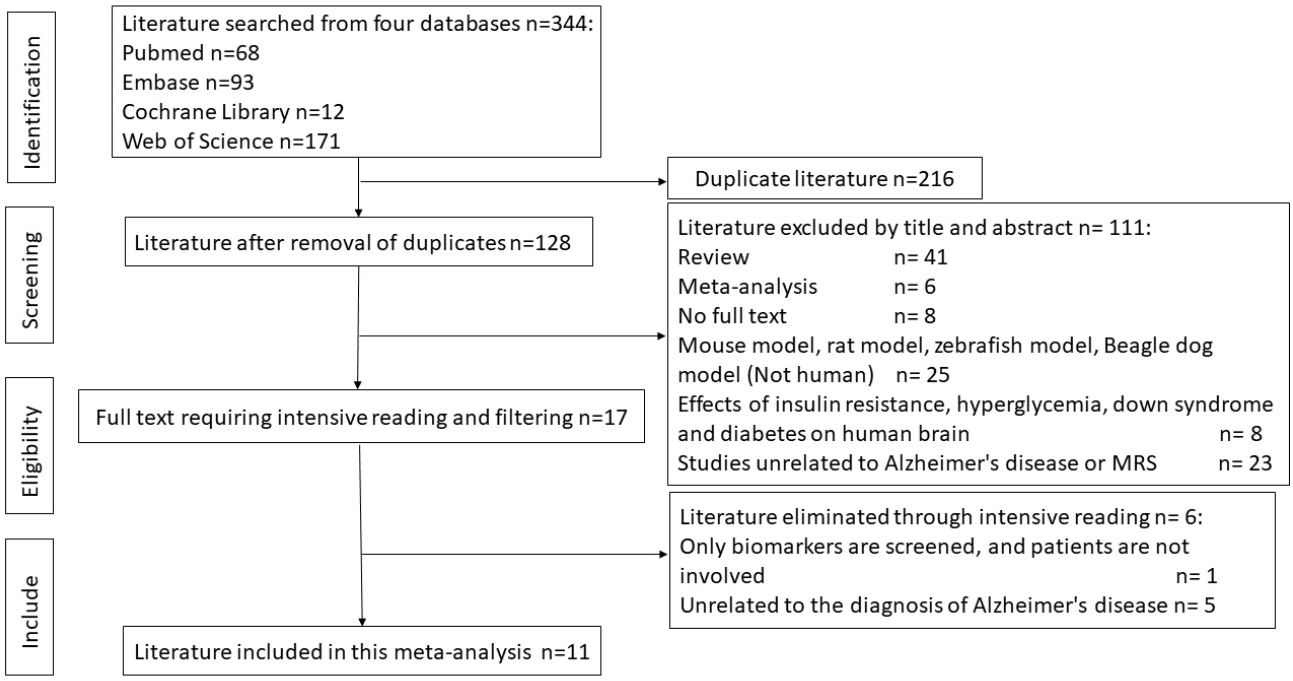

Fig. 1. Results of literature search and the process of literature selection. 344 articles on the diagnosis of Alzheimer's disease (AD) by magnetic resonance spectroscopy (MRS) detection biomarkers were obtained by searching 4 databases. After screening at various levels, 11 articles were finally included in the analysis.

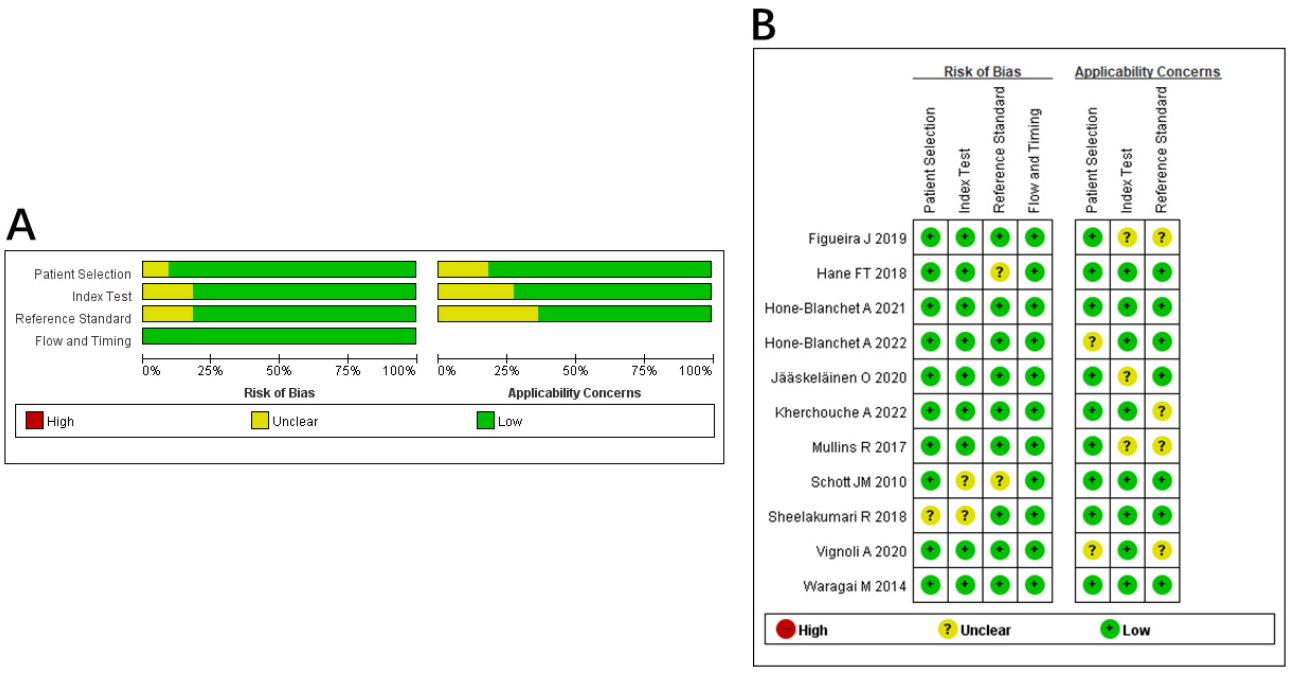

Fig. 2. The bias assessment of the 11 included articles using Revman 5.4. (A) The graph of risk of bias and applicability concerns, representing the reviewers' judgments about each domain as percentages across the included studies. (B) A summary of risk of bias and applicability concerns for each domain in every included study, using color coding: red for high, yellow for unclear, and green for low.

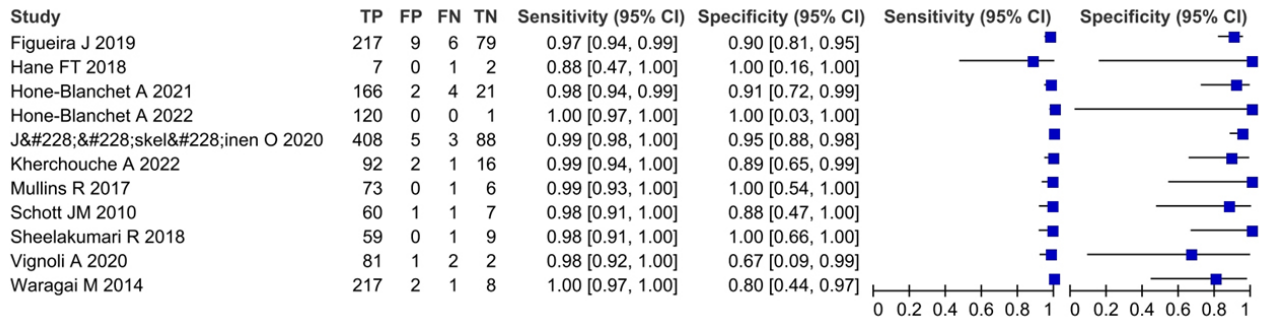

Fig. 3. Forest map. Values are shown with 95 per cent confidence intervals.

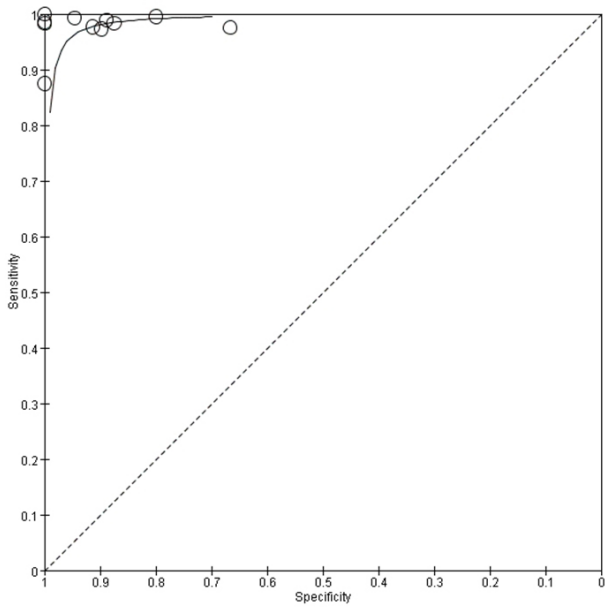

Fig. 4. Summary receiver operating characteristic (SROC) curve.

Established biomarkers of AD include amyloid β peptide (Aβ) [30], β-Site app cleaving enzyme 1 (BACE1), and amyloid-β oligomers [31]. Aβ, the main component of senile plaques (SPs), consists of polypeptides containing 36 to 43 amino acids. Aβ42 levels significantly decrease, even in the MCI stage, while Aβ40 levels remain unchanged, resulting in a decreased Aβ42/Aβ40 ratio [32]. Tau, the main component of neurofibrillary tangles (NFTs), is a neuronal microtubule-associated protein that stabilizes the microtubule network. In AD patients, tau protein is highly phosphorylated and prone to aggregation, leading to NFT formation, neuronal microtubule disruption, and neuron degeneration [33]. BACE1, the primary β-secretase, is a crucial enzyme in the amyloid precursor protein (APP) cleavage process.

In addition to the above biomarkers, plasma biomarkers of AD include β-amyloid in plasma, Apolipoprotein E (ApoE), Apolipoprotein J (APOJ), and APP in platelets [34]. The urine biomarker for AD is AD-associated neurofilament protein (AD7C NTP) [35]. Other AD biomarkers include advanced glycation end products (AGEs) and isoprostaglandins (IP) [36].

Currently, MRS is being utilized for the detection of biomarkers in patients with AD. Numerous AD-specific biomarkers have been identified, and multiple studies have demonstrated the significant diagnostic and therapeutic implications of these detection results. This study highlights the high accuracy of utilizing MRS for detecting AD biomarkers.

Meta-analysis of the selected literature reveals that the sensitivity and specificity of MRS detection methods are very close to 1, with all study results clustered in the upper left corner of the SROC curve. This indicates the promising clinical potential of MRS biomarkers in AD diagnosis.

For instance, Bolo NR *et al*. [37] employed proton MRS to assess the concentration of inositol in the ACC, and measured fasting blood glucose and insulin levels in 11 healthy individuals. Subsequently, a 60-minute hyperglycemic clamp test was conducted to maintain stable blood glucose levels while elevating plasma insulin concentrations. The results revealed a 9% reduction in inositol during the hyperinsulin-normoglycemic clamp, suggesting that elevated inositol levels may be attributed to decreased cerebral insulin levels or action, potentially associated with dysfunctional brain networks leading to cognitive or emotional disorders. Similarly, Matthews DC *et al*. [38] investigated the therapeutic effects of riluzole, a glutamate modulator, in 42 AD patients, of which 20 received placebo treatment only. Proton magnetic resonance spectroscopy was utilized to assess the neuronal vitality marker NAA, while magnetic resonance spectroscopy was employed to measure gluta-

mate levels in the cingulate gyrus of the brain. The results revealed a significant reduction in the decrease of local glucose metabolism index in the brain in the treatment group, indicating a notable improvement in the disorder of glutamate neural circuits.

Hone-Blanchet A *et al*. [15] explored the association between frontal metabolites and AD biomarkers in normal elderly individuals. They utilized proton magnetic resonance spectroscopy to assess frontal metabolites in 144 elderly subjects. The levels of gamma-aminobutyric acid (GABA+), inositol, and creatine (mI/tCr) in the frontal lobe of normal elderly individuals were found to be correlated with age. GABA+ levels decreased with age, while mI/tCr levels decreased with age. This study adds further evidence to the utility of MRS in investigating biomarkers related to aging, pathological aging, and AD. Kherchouche A *et al*. [16] conducted a comprehensive investigation on MRS-based neural network detection for early dementia and proposed an attention-guided supervised deep learning framework for early AD detection using 1H-MRS data. Their analysis of 1H-MRS samples from 33 normal controls, 49 patients with MCI caused by AD, and 29 patients with AD in university hospitals demonstrated that the framework achieved an accuracy of 95.23%, indicating the stable detection of early AD biomarkers associated with metabolite characteristics.

Avgerinos KI *et al*. [39] administered keto monoester (KME) treatment to 50 adults aged $\geq$55 years with cognitive intactness and metabolic syndrome. Participants consumed a drink containing 25 g KME three times a day for 28 days, following which the concentration of β-hydroxybutyrate (BHB) and various brain and muscle metabolites in the precuneus were measured using MRS. The results indicated that oral KME could safely induce severe ketosis, enhance brain ketosis, and improve cognitive abilities, with significant relevance to AD. Insel PS *et al*. [40] investigated the relationship between ApoEε2 and ε4, age, and amyloid beta in cognitively unimpaired adults. Their findings suggested that the presence of the ApoEε2 allele suppressed amyloid beta deposition in individuals carrying the ApoEε4 risk allele. Ballarini T *et al*. [41] conducted a longitudinal study on cognitive impairment and dementia, examining the relationship between the Mediterranean diet, AD biomarkers, and brain atrophy in elderly individuals. Their study, which included 169 cognitively normal participants, 53 relatives with AD, 209 patients with subjective cognitive decline, and 81 patients with MCI, revealed that adherence to the Mediterranean diet was associated with a protective effect against memory loss and middle temporal lobe atrophy, along with significant reductions in amyloid and tau proteins in the brain.

The biomarkers detected through MRS serve as effective evidence for diagnosing MCI, enabling the early prediction of AD and providing valuable insights to potential patients for implementing preventive measures in their daily lives.

Hone-Blanchet A *et al*. [17] conducted 3T voxel magnetic resonance imaging of the medial frontal cortex in 120 elderly women with normal cognition and women with MCI. The results indicated a decrease in γ-aminobutyric acid (GABA+) levels in the frontal lobe of women with MCI, highlighting a strong correlation between frontal lobe GABA+ levels and neural aging.

Talwar P *et al*. [42] conducted a meta-analysis on various imaging examinations of AD, focusing on the quantitative and/or functional data of neuroimaging patterns in MCI and/or AD. Notably, consistent bilateral destruction of the precuneus lobe, medial temporal lobe, and limbic system was observed in functional magnetic resonance imaging among AD patients. Diffusion tensor imaging (DTI) confirmed atrophic changes in the corpus callosum observed in MCI and AD patients, while molecular imaging revealed variable metabolite concentrations in the posterior cingulate cortex (PCC). These findings underscore the potential for more accurate AD diagnosis through multiple neuroimaging methods.

Biomarkers have increasingly become pivotal indicators for AD diagnosis, with biomarker research emerging as a significant focus of study. Tao Q *et al*. [43] investigated the relationship between C-reactive protein and ApoE genotypes, as well as cognitive function and AD biomarkers. Their study included 566 participants, of whom 222 carried one risk allele and 70 were homozygous carriers of two risk alleles. The results demonstrated a correlation between increased C-reactive protein (CRP) levels and elevated total tau protein and phosphorylated tau protein levels in cerebrospinal fluid. It was concluded that C-reactive protein released due to peripheral blood inflammation may serve as a biomarker for AD and a potential therapeutic target for the disease. Kivimäki M *et al*. [44] examined the relationship between cognitive stimulation in the workplace and subsequent dementia risk in a study involving 110,000 participants. Through statistical analysis of participant data and levels of nerve growth guidance factor homolog 2, carbohydrate sulfotransferase (CHSTC), and peptide glycine Adrenomyeloneuropathy (AMD) in the central nervous system, it was determined that individuals engaged in cognitively stimulating work had a lower risk of dementia.

Positron Emission Tomography-Computed Tomography (PET-CT) imaging can also detect biomarkers of AD

and is a novel detection method known for its high accuracy. La Joie R *et al*. [45] investigated the clinical manifestations of AD, the presence of the ApoE ε4 allele, and the association of AD with β-amyloid and tau protein loads [18,45,46]. They studied 119 β-amyloid positive symptomatic AD patients and found that the clinical phenotype of AD was associated with different distribution patterns of tau protein but not amyloid protein. Age and the ApoE ε4 genotype were identified as risk factors for AD [19–21,47].

Vignoli *et al*. [22] evaluated the relationship between the incidence rate of AD and factors such as age, sex, ApoE ε4 genotype, and clinical diagnosis. They recruited 166 elderly individuals with normal cognitive function, 77 patients with MCI, and 62 dementia patients clinically diagnosed with AD. After performing amyloid PET and tau protein detection in the brain via PET imaging, the results indicated a strong correlation between AD dementia and biomarker-labeled PET examination.

Despite yielding significant results, this study has several limitations. Firstly, the small number of selected articles and limited sample sizes may introduce selection bias. Secondly, the scope of the study is restricted, potentially failing to comprehensively cover all relevant literature, thus limiting the generalizability of the results. Additionally, methodological differences among studies may affect result consistency.

Therefore, future research should focus on increasing sample sizes and considering differences among different populations. Furthermore, comparing different study methods is necessary to determine the optimal biomarker detection strategy. Finally, standardizing and normalizing MRS techniques is crucial to ensure their robustness and reliability in clinical practice.

Conclusion

The detection of biomarkers by MRS demonstrates feasibility and high accuracy in diagnosing AD. This technology holds promise for widespread application in the clinical diagnosis of AD in the future.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

BW designed the study. BW wrote the manuscript. YQX, YD, JZ, FFZ, and CLW performed the experiments, and YPL arranged the data. All authors contributed to editing changes in the manuscript. All authors read and approved the final manuscript. All authors have sufficiently participated in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62641/aep.v52i2.1552.

References

[1] Bagheri-Mohammadi S. Stem cell-based therapy as a promising approach in Alzheimer's disease: current perspectives on novel treatment. Cell and Tissue Banking. 2021; 22: 339–353.

[2] Chai FX, Wang YM. Exploring the Impact of Sirt1 on Oxidative Stress and Inflammation in Alzheimer's Disease Cell Models Through p53 Regulation: A Preliminary Study. Journal of Biological Regulators and Homeostatic Agents. 2023; 37: 3739–3750.

[3] Spina S, La Joie R, Petersen C, Nolan AL, Cuevas D, Cosme C, *et al*. Comorbid neuropathological diagnoses in early versus late-onset Alzheimer's disease. Brain: a Journal of Neurology. 2021; 144: 2186–2198.

[4] Moon W, Han JW, Bae JB, Suh SW, Kim TH, Kwak KP, *et al*. Disease Burdens of Alzheimer's Disease, Vascular Dementia, and Mild Cognitive Impairment. Journal of the American Medical Directors Association. 2021; 22: 2093–2099.e3.

[5] Naudé PJW, Ramakers IHGB, van der Flier WM, Jiskoot LC, Reesink FE, Claassen JAHR, *et al*. Serum and cerebrospinal fluid Neutrophil gelatinase-associated lipocalin (NGAL) levels as biomarkers for the conversion from mild cognitive impairment to Alzheimer's disease dementia. Neurobiology of Aging. 2021; 107: 1–10.

[6] Grimmer T. Therapy Developments in Alzheimer's Disease. Fortschritte der Neurologie-Psychiatrie. 2022; 90: 352–360. (In German)

[7] Mahaman YAR, Embaye KS, Huang F, Li L, Zhu F, Wang JZ, *et al*. Biomarkers used in Alzheimer's disease diagnosis, treatment, and prevention. Ageing Research Reviews. 2022; 74: 101544.

[8] Monge-García V, García-Ayllón MS, Sáez-Valero J, Sánchez-Payá J, Navarrete-Rueda F, Manzanares-Robles J, *et al*. Relation between Alpha-Synuclein and Core CSF Biomarkers of Alzheimer's Disease. Medicina (Kaunas, Lithuania). 2021; 57: 954.

[9] Yilmaz A, Ustun I, Ugur Z, Akyol S, Hu WT, Fiandaca MS, *et al*. A Community-Based Study Identifying Metabolic Biomarkers of Mild Cognitive Impairment and Alzheimer's Disease Using Artificial Intelligence and Machine Learning. Journal of Alzheimer's Disease: JAD. 2020; 78: 1381–1392.

[10] Piersson AD, Mohamad M, Rajab F, Suppiah S. Cerebrospinal Fluid Amyloid Beta, Tau Levels, Apolipoprotein, and ^{1}H-MRS Brain Metabolites in Alzheimer's Disease: A Systematic Review. Academic Radiology. 2021; 28: 1447–1463.

[11] Song T, Song X, Zhu C, Patrick R, Skurla M, Santangelo I, *et al*. Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of Alzheimer's disease: A meta-analysis of in vivo magnetic resonance spectroscopy studies. Ageing Research Reviews. 2021; 72: 101503.

[12] Fernández-Vega N, Ramos-Rodriguez JR, Alfaro F, Barbancho MÁ, García-Casares N. Usefulness of magnetic resonance spectroscopy in mesial temporal sclerosis: a systematic review. Neuroradiology. 2021; 63: 1395–1405.

[13] Hekimoglu A, Ergun O, Turan A, Taskin Turkmenoglu T, Hekimoglu B. Role of magnetic resonance spectroscopy in differential diagnosis of solitary pulmonary lesions. Diagnostic and Interventional Radiology (Ankara, Turkey). 2021; 27: 710–715.

[14] Quintero ME, Pontes JGDM, Tasic L. Metabolomics in degenerative brain diseases. Brain Research. 2021; 1773: 147704.

[15] Hone-Blanchet A, Bohsali A, Krishnamurthy LC, Shahid S, Lin Q, Zhao L, *et al*. Relationships between frontal metabolites and Alzheimer's disease biomarkers in cognitively normal older adults. Neurobiology of Aging. 2022; 109: 22–30.

[16] Kherchouche A, Ben-Ahmed O, Guillevin C, Tremblais B, Julian A, Fernandez-Maloigne C, *et al*. Attention-guided neural network for early dementia detection using MRS data. Computerized Medical Imaging and Graphics: the Official Journal of the Computerized Medical Imaging Society. 2022; 99: 102074.

[17] Hone-Blanchet A, Bohsali A, Krishnamurthy LC, Shahid SS, Lin Q, Zhao L, *et al*. Frontal Metabolites and Alzheimer's Disease Biomarkers in Healthy Older Women and Women Diagnosed with Mild Cognitive Impairment. Journal of Alzheimer's Disease: JAD. 2022; 87: 1131–1141.

[18] Figueira J, Adolfsson R, Nordin Adolfsson A, Nyberg L, Öhman A. Serum Metabolite Markers of Dementia Through Quantitative NMR Analysis: The Importance of Threonine-Linked Metabolic Pathways. Journal of Alzheimer's Disease: JAD. 2019; 69: 763–774.

[19] Jääskeläinen O, Hall A, Tiainen M, van Gils M, Lötjönen J, Kangas AJ, *et al*. Metabolic Profiles Help Discriminate Mild Cognitive Impairment from Dementia Stage in Alzheimer's Disease. Journal of Alzheimer's Disease: JAD. 2020; 74: 277–286.

[20] Sheelakumari R, Sarma SP, Kesavadas C, Thomas B, Sasi D, Sarath LV, *et al*. Multimodality Neuroimaging in Mild Cognitive Impairment: A Cross-sectional Comparison Study. Annals of Indian Academy of Neurology. 2018; 21: 133–139.

[21] Hane FT, Li T, Plata JA, Hassan A, Granberg K, Albert MS. Inhaled Xenon Washout as a Biomarker of Alzheimer's Disease. Diagnostics (Basel, Switzerland). 2018; 8: 41.

[22] Vignoli A, Paciotti S, Tenori L, Eusebi P, Biscetti L, Chiasserini D, *et al*. Fingerprinting Alzheimer's Disease by ^{1}H Nuclear Magnetic Resonance Spectroscopy of Cerebrospinal Fluid. Journal of Proteome Research. 2020; 19: 1696–1705.

[23] Waragai M, Hata S, Suzuki T, Ishii R, Fujii C, Tokuda T, *et al*. Utility of SPM8 plus DARTEL (VSRAD) combined with magnetic resonance spectroscopy as adjunct techniques for screening and predicting dementia due to Alzheimer's disease in clinical practice. Journal of Alzheimer's Disease: JAD. 2014; 41: 1207–1222.

[24] Schott JM, Frost C, MacManus DG, Ibrahim F, Waldman AD, Fox NC. Short echo time proton magnetic resonance spectroscopy in Alzheimer's disease: a longitudinal multiple time point study. Brain. 2010; 133: 3315–3322.

[25] Mullins R, Reiter D, Kapogiannis D. Magnetic resonance spectroscopy reveals abnormalities of glucose metabolism in the Alzheimer's brain. Annals of Clinical and Translational Neurology. 2018; 5: 262–272.

[26] Yin X, Qiu Y, Zhao C, Zhou Z, Bao J, Qian W. The Role of Amyloid-Beta and Tau in the Early Pathogenesis of Alzheimer's Disease. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2021; 27: e933084.

[27] Lemke G, Huang Y. The dense-core plaques of Alzheimer's disease are granulomas. The Journal of Experimental Medicine. 2022; 219: e20212477.

[28] Ge XY, Cui K, Liu L, Qin Y, Cui J, Han HJ, *et al*. Screening and predicting progression from high-risk mild cognitive impairment to Alzheimer's disease. Scientific Reports. 2021; 11: 17558.

[29] Leuzy A, Smith R, Cullen NC, Strandberg O, Vogel JW, Binette AP, *et al*. Biomarker-Based Prediction of Longitudinal Tau Positron Emission Tomography in Alzheimer Disease. JAMA Neurology. 2022; 79: 149–158.

[30] Jeremic D, Jiménez-Díaz L, Navarro-López JD. Past, present and future of therapeutic strategies against amyloid-β peptides in Alzheimer's disease: a systematic review. Ageing Research Reviews. 2021; 72: 101496.

[31] Nicsanu R, Cervellati C, Benussi L, Squitti R, Zanardini R, Rosta V, *et al*. Increased Serum Beta-Secretase 1 Activity is an Early Marker of Alzheimer's Disease. Journal of Alzheimer's Disease: JAD. 2022; 87: 433–441.

[32] Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, *et al*. The Amyloid-β Pathway in Alzheimer's Disease. Molecular Psychiatry. 2021; 26: 5481–5503.

[33] Thijssen EH, La Joie R, Strom A, Fonseca C, Iaccarino L, Wolf A, *et al*. Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. The Lancet. Neurology. 2021; 20: 739–752.

[34] Teunissen CE, Verberk IMW, Thijssen EH, Vermunt L, Hansson O, Zetterberg H, *et al*. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. The Lancet. Neurology. 2022; 21: 66–77.

[35] Giri B, Seamon M, Banerjee A, Chauhan S, Purohit S, Morgan J, *et al*. Emerging urinary alpha-synuclein and miRNA biomarkers in Parkinson's disease. Metabolic Brain Disease. 2022; 37: 1687–1696.

[36] Zhou R, Ji B, Kong Y, Qin L, Ren W, Guan Y, *et al*. PET Imaging of Neuroinflammation in Alzheimer's Disease. Frontiers in Immunology. 2021; 12: 739130.

[37] Bolo NR, Jacobson AM, Musen G, Simonson DC. Hyperglycemia and hyperinsulinemia effects on anterior cingulate cortex myoinositol-relation to brain network functional connectivity in healthy adults. Journal of Neurophysiology. 2022; 127: 1426–1437.

[38] Matthews DC, Mao X, Dowd K, Tsakanikas D, Jiang CS, Meuser C, *et al*. Riluzole, a glutamate modulator, slows cerebral glucose metabolism decline in patients with Alzheimer's disease. Brain: a Journal of Neurology. 2021; 144: 3742–3755.

[39] Avgerinos KI, Mullins RJ, Egan JM, Kapogiannis D. Ketone Ester Effects on Biomarkers of Brain Metabolism and Cognitive Performance in Cognitively Intact Adults $\geq$ 55 Years Old. A Study Protocol for a Double-Blinded Randomized Controlled Clinical Trial. The Journal of Prevention of Alzheimer's Disease. 2022; 9: 54–66.

[40] Insel PS, Hansson O, Mattsson-Carlgren N. Association Between Apolipoprotein E ε2 vs ε4, Age, and β-Amyloid in Adults Without Cognitive Impairment. JAMA Neurology. 2021; 78: 229–235.

[41] Ballarini T, Melo van Lent D, Brunner J, Schröder A, Wolfsgruber S, Altenstein S, *et al*. Mediterranean Diet, Alzheimer Disease Biomarkers and Brain Atrophy in Old Age. Neurology. 2021; 96: e2920–e2932.

[42] Talwar P, Kushwaha S, Chaturvedi M, Mahajan V. Systematic Review of Different Neuroimaging Correlates in Mild Cognitive Impairment and Alzheimer's Disease. Clinical Neuroradiology. 2021; 31: 953–967.

[43] Tao Q, Alvin Ang TF, Akhter-Khan SC, Itchapurapu IS, Killiany R, Zhang X, *et al*. Impact of C-Reactive Protein on Cognition and Alzheimer Disease Biomarkers in Homozygous *APOE* ε4 Carriers. Neurology. 2021; 97: e1243–e1252.

[44] Kivimäki M, Walker KA, Pentti J, Nyberg ST, Mars N, Vahtera J, *et al*. Cognitive stimulation in the workplace, plasma proteins, and risk of dementia: three analyses of population cohort studies. BMJ (Clinical Research Ed.). 2021; 374: n1804.

[45] La Joie R, Visani AV, Lesman-Segev OH, Baker SL, Edwards L, Iaccarino L, *et al*. Association of *APOE4* and Clinical Variability in Alzheimer Disease With the Pattern of Tau- and Amyloid-PET. Neurology. 2021; 96: e650–e661.

[46] Therriault J, Pascoal TA, Benedet AL, Tissot C, Savard M, Chamoun M, *et al*. Frequency of Biologically Defined Alzheimer Disease in Relation to Age, Sex, *APOE* ε4, and Cognitive Impairment. Neurology. 2021; 96: e975–e985.

[47] Das N, Ren J, Spence JS, Rackley A, Chapman SB. Relationship of Parieto-Occipital Brain Energy Phosphate Metabolism and Cognition Using ^{31}P MRS at 7-Tesla in Amnestic Mild Cognitive Impairment. Frontiers in Aging Neuroscience. 2020; 12: 222.