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RESEARCH ARTICLE

ROLE OF RADIO DIAGNOSIS IN EARLY DETECTION OF ALZHEIMER’S DISEASE:A SYSTEMATIC REVIEW

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Abstract

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Alzheimer’s disease (AD) represents the most prevalent form of dementia, affecting millions worldwide and posing significant public health challenges.Early detection remains critical for initiating timely interventions that may mitigatedisease progression, particularly during preclinical or mild cognitive impairment (MCI) stages. Radio diagnostic modalities, including Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Diffusion Tensor Imaging (DTI), and emerging techniques like arterial spin labeling (ASL), providen – invasive tools to identify structural, functional, and molecular brain changes associated with AD. This systematic review synthesizes evidence from peer-reviewed literature to evaluate the role of these imaging modalities in early AD detection, emphasizing their diagnostic capabilities, clinical applications, and integration with other biomarkers.Following the PRISMA framework, the review identifies key modalities suchas structural MRI for detecting hippocampal atrophy, amyloid-PET for visualizing pathological protein aggregates, and functional MRI for assessing connectivity disruptions. The review also explores challenges in standardization, accessibility, and cost, alongside future directions involving artificial intelligence and novel imaging tracers.Comprehensive visual aids, including flowcharts and schematic diagrams, illustrate imaging workflows and diagnostic frameworks.

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Introduction:-

Alzheimer’s disease (AD) constitutes a progressive neurodegenerative disorder, accounting for 60–80% of dementia cases globally, with over 50 million individuals affected (1). The disease manifests through memory loss, cognitive decline, and impaired daily functioning, leading to substantial socioeconomic burdens. Prevalence is projected to triple by 2050, underscoring the urgency of effective diagnostic strategies (2). Early detection, particularly during preclinical or mild cognitive impairment (MCI) stages, enables interventions that may delay progression, such as pharmacological therapies or lifestyle modifications (3). Traditional clinical

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assessments, including the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), often lack sensitivity for detecting subtle changes in early AD (4). Radiodiagnostic modalities, encompassing Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Diffusion Tensor Imaging (DTI), and emerging techniques, offer objective, quantifiable biomarkers by visualizing AD-specific neuropathology, such as cortical atrophy, amyloid-beta plaques, tau tangles, and connectivity disruptions (5). These tools have transformed the diagnostic landscape, enabling earlier and more accurate identification of AD. This systematic review synthesizes current evidence on the role of radiodiagnosis in early AD detection, highlighting the capabilities of established and emerging modalities, their clinical utility, and challenges in implementation. The review adheres to the PRISMA framework to ensure transparency and rigor, incorporating visual aids to clarify imaging workflows and diagnostic processes.

Methods

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a structured, transparent, and reproducible approach to literature synthesis (6). The methodology encompassed literature search, study selection, data extraction, and qualitative synthesis, as detailed below.

LiteratureSearch

A comprehensive search was performed across electronic databases, including PubMed, Scopus, Web of Science, Embase, Cochrane Library, and PsycINFO, covering publications from January 2000 to December 2024.Search terms included combinations of keywordsandMeSHterms,suchas“Alzheimer’sdisease,”“earlydetection,”“radiodiagnosis,”“neuroimaging,”“magneticresonanceimaging,”“positronemissiontomography,” “diffusion tensor imaging,” “amyloid imaging,” “tau imaging,” “functional MRI,” “arterial spin labeling,” “magnetic resonance spectroscopy,” and “quantitative susceptibility mapping.”Boolean operators (AND, OR, NOT) were employed to refine the search strategy.Additionalsources,includingreferencelistsofrelevantreviews,conferenceproceedings,andgreyliterature(e.g.,technicalreports,theses),weremanuallysearched to identify studies not captured by electronic databases.The search was updated in December 2024 to include the most recent publications.

InclusionandExclusionCriteria

Studies were included if they met the following criteria:(1) peer-reviewed articles published in English; (2) focus on radiodiagnostic modalities (MRI, PET, DTI, ASL, MRS, QSM, or other neuroimaging techniques) for early AD detection, including preclinical or MCI stages; (3) involvement of human participants; and (4) reporting diagnostic performancemetrics,clinicalapplications,technicaladvancements,orchallenges. Exclusion criteriaincluded:(1)non-humanstudies;(2)studiesfocusingexclusivelyonadvancedAD or non-AD dementias; (3) case reports, editorials, letters, or opinion pieces; (4) studieslackingdetaileddescriptionsofimagingprotocolsoroutcomes;and(5)non-Englishpublications.StudiesinvolvingmixeddementiapopulationswereincludedonlyifAD-specific findings were clearly delineated.

Study Selection

The search yielded 5,472 articles, which were imported into EndNote X9 for deduplication.After removing duplicates, 3,214 articles remained.Titles and abstracts were independently screened by two reviewers using predefined criteria, resulting in 632 articles for full-text review.Following full-text assessment, 126 studies were included in the final synthesis.Discrepancies between reviewers were resolved through consensus or consultation with a third reviewer.The PRISMA flowchart below illustrates the study selection process, detailing the number of records at each stage.

Data Extraction

Data were extracted using a standardized template, capturing: (1) study characteristics (author, year, study design, sample size, country); (2) imaging modalities (e.g., MRI, PET,DTI,ASL,MRS, QSM);(3)participantdemographics (e.g., preclinical, MCI,early AD, controls; age, sex); (4) diagnostic performance metrics (e.g., sensitivity, specificity, area under the curve); (5) clinical applications (e.g., screening, differential diagnosis, longitudinal monitoring); (6) technical advancements (e.g., novel tracers, AI-based analysis); and (7) reported challenges (e.g., cost, accessibility, standardization).Data were synthesizedqualitatively, identifyingthematicpatternsacrossmodalities, theirdiagnostic capabilities, and their integration in clinical practice.

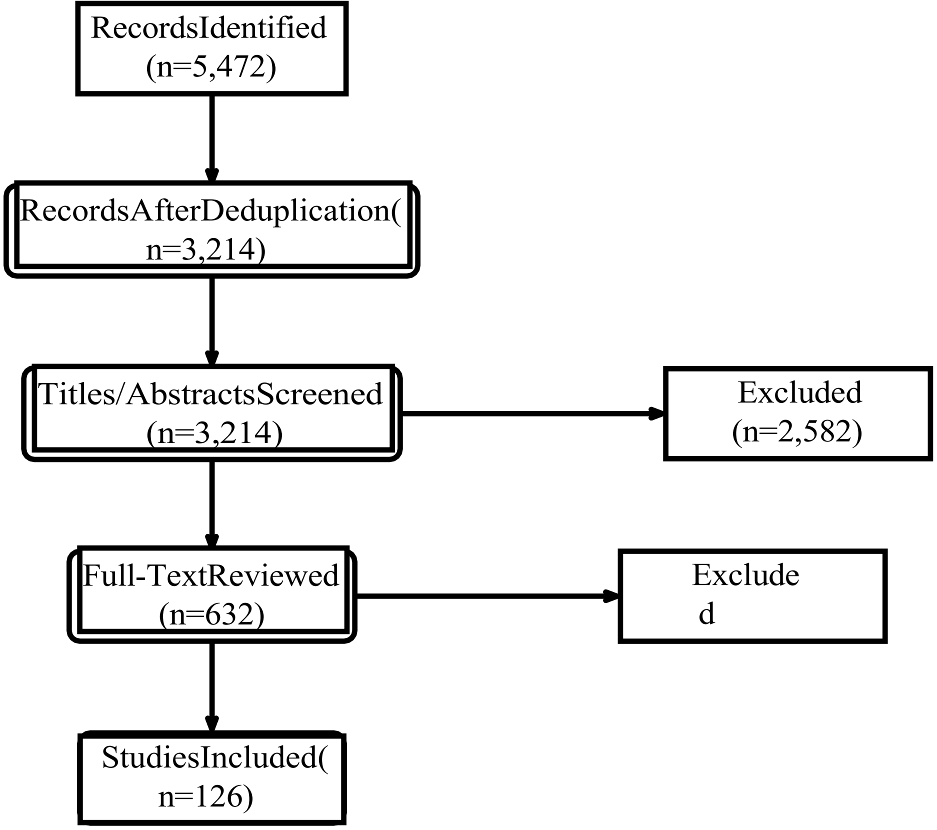

Figure1:PRISMAflowchartofstudyselectionprocessforsystematicreview.

QualityAssessment

The quality of included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, focusing on risk of bias and applicability concerns (7). Domains evaluated included patient selection, index test (imaging modality), reference standard (e.g., NIA-AA criteria), and flow/timing. Studies with low risk of bias and high applicability to early AD detection were prioritized in the synthesis.

Radio diagnostic Modalities for Early AD Detection

Radiodiagnostic modalities have transformed early AD detection by providing detailed insights into structural, functional, molecular, and microstructural brain changes.The following subsections describe the primary modalities, their diagnostic capabilities, clinical applications, and technical considerations, supported by evidence from the reviewed literature.

Structural Magnetic Resonance Imaging(MRI)

Structural MRI, performed using 1.5T or 3T scanners, is a cornerstone of AD imaging due to its widespread availability, non-invasive nature, and ability to detect brain atrophy (8). The hippocampus, entorhinal cortex, and medial temporal lobe exhibit early volume loss in preclinical and MCI stages, making them critical regions of interest. T1-weighted sequences provide high-resolution images for volumetric analysis, while T2-weighted and Fluid-Attenuated Inversion Recovery (FLAIR) sequences help differentiate AD from alternative pathologies, such as vascular dementia, tumors, or hydrocephalus. Software tools like FreeSurfer, FSL, and SPM enable quantitative assessment of hippocampal volume, cortical thickness, and subcortical structures, which serve as robust biomarkers (9). Voxel-based morphometry (VBM) and surface-based analysis further enhance detection of subtle atrophy patterns. Structural MRI's compatibility with longitudinal monitoring and lack of ionizing radiation make it ideal for repeated assessments in clinical and research settings. The modality's accessibility facilitates its use in diverse healthcare settings, including resource-limited regions.

Figure2:SchematicworkflowforstructuralMRIprocessinginADdetection.

Functional Magnetic Resonance Imaging (fMRI)

Functional MRI, particularly resting-state fMRI, assesses brain connectivity, focusing on the default mode network (DMN), which includes the posterior cingulate cortex, precuneus, medial prefrontal cortex, and angular gyrus (10). The DMN is integral to memory consolidation and cognitive processing, and its disruption is an early marker of AD, observable in preclinical and MCI stages. Resting-state fMRI measures blood-oxygen-level-dependent (BOLD) signals to map functional connectivity, revealing reduced coherence in AD-related networks. Task-based fMRI, though less common, evaluates cognitive processing deficits during memory or attention tasks. The modality's ability to detect subtle connectivity changes complements structural MRI, providing a comprehensive view of brain alterations. Advanced analysis techniques, such as graph theory and independent component analysis (ICA), enhance the characterization of network disruptions (11). Functional MRI's sensitivity to early pathological changes support its role in preclinical diagnosis, though its susceptibility to motion artifacts and variability across scanners necessitates rigorous standardization.

Positron Emission Tomography (PET)

PET imaging encompasses amyloid-PET, tau-PET, and FDG-PET, each targeting distinct AD pathologies with high molecular specificity. Amyloid-PET, utilizing tracers such as [18F]Florbetapir, [11C]Pittsburgh Compound B (PiB), or [18F]Florbetaben, visualizes amyloid-beta plaques, a hallmark of AD (12). The standardized uptake value ratio (SUVR) quantifies amyloid burden, enabling differentiation of AD from other dementias, such as frontotemporal dementia or dementia with Lewy bodies. Tau-PET, with tracers like [18F]Flortaucipir or [18F]MK-6240, detects neurofibrillary tangles, which correlate closely with cognitive decline and disease severity (13). FDG-PET measures cerebral glucose metabolism, revealing characteristic temporoparietal and posterior cingulate hypometabolism in AD (14). PET's ability to detect molecular changes before structural alterations enhances its diagnostic value, particularly in ambiguous cases.

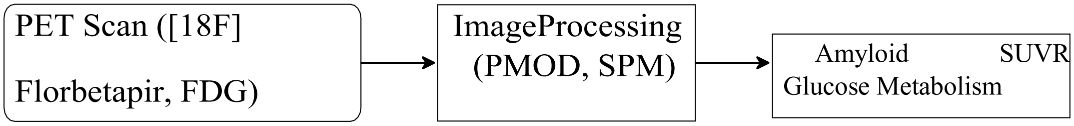

Figure 3:Schematic workflow for PET imaging in AD detection.

Diffusion Tensor Imaging(DTI)

Diffusion Tensor Imaging (DTI) evaluates white matter integrity by measuring fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), which reflect axonal and myelin integrity (15). White matter tracts, such as the fornix, cingulum, uncinate fasciculus, and corpus callosum, show early disruptions in AD, detectable in preclinical and MCI stages. DTI complements structural MRI by providing insights into microstructural changes that precede gross atrophy. Advanced processing tools, such as FSL, Tract-Based Spatial Statistics (TBSS), and diffusion kurtosis imaging (DKI), enable quantitative analysis of white matter tracts. The modality's sensitivity to early pathological changes enhance its potential as an adjunctive tool in AD diagnosis, particularly for detecting connectivity disruptions not visible on standard MRI.

Emerging Neuroimaging Techniques

Emerging modalities, including arterial spin labeling (ASL), magnetic resonance spectroscopy (MRS), quantitative susceptibility mapping (QSM), and susceptibility-weighted imaging (SWI), offer additional diagnostic insights. ASL measures cerebral blood flow non-invasively using magnetically labeled arterial blood as an endogenous tracer, revealing hypoperfusion in AD-affected regions, such as the posterior cingulate, precuneus, and parietal cortex (16). MRS detects metabolic alterations, such as reduced N-acetyl aspartate (NAA), increased myo-inositol (mI), and altered choline levels, which reflect neuronal loss, gliosis, and membrane turnover (17). QSM quantifies iron deposition in regions like the hippocampus and basal ganglia, which may contribute to AD pathology. SWI detects microhemorrhages and vascular abnormalities, aiding differential diagnosis from vascular dementia. These modalities, while not yet standard in clinical practice, are increasingly incorporated into research protocols to enhance diagnostic specificity.

Multimodal Imaging Approaches

Multimodal imaging, combining structural MRI, fMRI, PET, DTI, and emerging techniques, provides a comprehensive assessment of AD pathology (18). For example, structural MRI identifies atrophy, amyloid-PET confirms pathological protein aggregates, FDG-PET reveals metabolic deficits, and fMRI detects connectivity disruptions. Integrating imaging with CSF biomarkers (e.g., amyloid-beta 42, total tau, phosphorylated tau) or blood-based biomarkers (e.g., p-tau181, p-tau217, neurofilament light) enhances diagnostic accuracy (19). Advanced analysis platforms, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) pipelines, facilitate multimodal data integration, enabling personalized diagnostic and prognostic models.

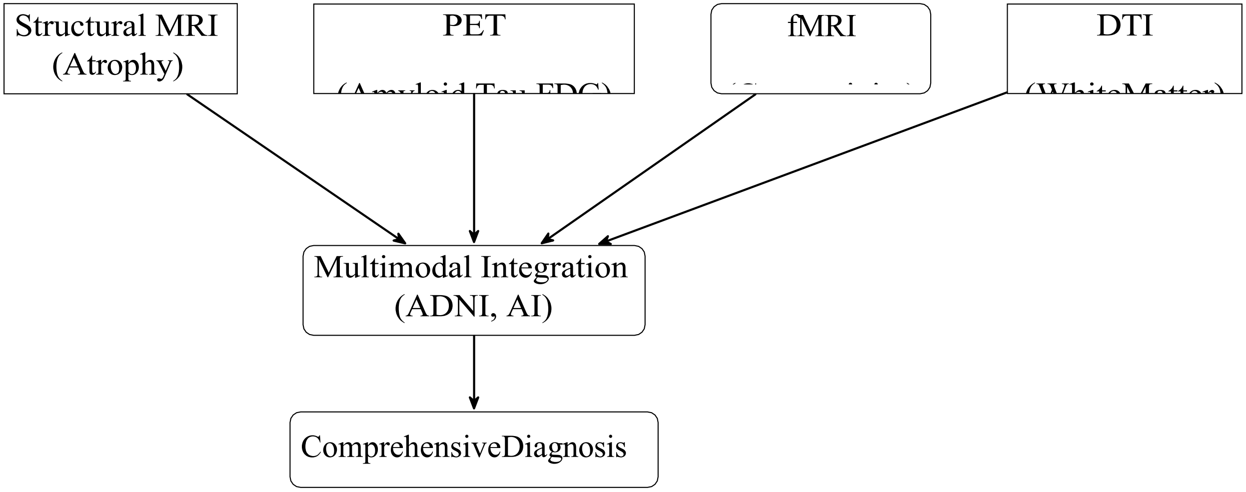

Figure4: Schematicofmulti-modalimagingintegrationforADdiagnosis.

ClinicalApplications

Radiodiagnostic modalities have diverse clinical applications in early AD detection. Structural MRI serves as a primary screening tool due to its accessibility, non-invasive nature, and ability to detect hippocampal and medial temporal lobe atrophy, guiding initial diagnostic workups (8). Amyloid-PET and tau-PET provide high specificity for confirming AD pathology, particularly in atypical presentations or when differentiating AD from other dementias, such as frontotemporal dementia, dementia with Lewy bodies, or vascular dementia (12, 13). FDG-PET identifies characteristic metabolic patterns, aiding differential diagnosis and monitoring disease progression (14). Functional MRI, though primarily a research tool, supports early detection by identifying connectivity disruptions in preclinical stages (10). DTI enhances diagnostic precision by detecting white matter changes, particularly in cases with atypical structural findings (15).

Technical Advancements

Recent technical advancements have enhanced the diagnostic capabilities of radiodiagnostic modalities. High-field MRI scanners (e.g., 7T) offer superior resolution for detecting subtle atrophy and microstructural changes (20). Novel PET tracers, such as [18F]NAV4694 for amyloid and [18F]RO948 for tau, improve binding specificity and signal-to-noise ratios (21). AI and machine learning algorithms, including convolutional neural networks (CNNs) and support vector machines (SVMs), automate image analysis, identifying patterns of atrophy, connectivity disruptions, or molecular changes with high accuracy (22). Deep learning models, trained on large datasets like ADNI, enable early detection and longitudinal monitoring. Cloud-based platforms facilitate data sharing and standardized processing, addressing variability across centers. Portable MRI systems and low-field scanners are being developed to improve access in underserved regions, while advances in ASL and QSM enhance non-invasive assessment of perfusion and iron deposition.

Challenges and Considerations

Radiodiagnostic modalities face several challenges that impact clinical adoption. PET imaging, particularly amyloid-PET and tau-PET, is costly (approximately $3,000–$5,000 per scan) and limited to specialized centers, restricting access in low- and middle-income countries (23). MRI, while more accessible, requires standardized acquisition protocols (e.g., ADNI harmonized protocols) to minimize variability across scanners and centers (24). Advanced modalities like DTI, fMRI, and QSM demand expertise in image acquisition and analysis, as well as high-quality scanners, which may not be available in all settings. Patient-related factors, such as motion artifacts, claustrophobia, or contraindications (e.g., pacemakers, metallic implants), can affect image quality. Ethical considerations arise in preclinical diagnosis, as positive imaging findings may prompt interventions or lifestyle changes without guaranteed therapeutic benefits (25). Cultural and socioeconomic factors, including healthcare disparities and patient awareness, further influence access to radiodiagnostic tools.

Future Directions

The future of radiodiagnosis in early AD detection is promising, driven by technological and scientific advancements. Artificial intelligence and machine learning will play a central role, with deep learning models improving diagnostic accuracy by identifying subtle patterns in imaging data (22). Novel PET tracers, targeting tau, neuroinflammation (e.g., TSPO ligands), or synaptic density (e.g., [11C]UCB-J), will enhance molecular specificity (26). Blood-based biomarkers, such as plasma p-tau217, neurofilament light (NfL), and glial fibrillary acidic protein (GFAP), offer cost-effective screening tools, potentially reducing reliance on expensive imaging (27). Integration of imaging and biomarkers through multi-omics platforms will enable personalized diagnostic and prognostic models. Portable MRI systems, low-field scanners, and point-of-care imaging devices will improve access in underserved regions. Global initiatives, such as ADNI, the European Prevention of Alzheimer's Dementia (EPAD) consortium, and the Global Alzheimer's Platform, aim to standardize imaging protocols, facilitate data sharing, and accelerate clinical translation (28). Advances in radiomics and connect omics will further elucidate AD pathophysiology, supporting the development of targeted therapies.

Conclusion

Radiodiagnostic modalities, including structural MRI, functional MRI, PET, DTI, and emergingtechniqueslikeASL,MRS,andQSM,arepivotalinearlyADdetection,providing objective biomarkers of structural, functional, molecular, and microstructural brain changes.Structural MRI excels in detecting hippocampal and medial temporal lobe atrophy, amyloid-PETandtau-PETofferhighspecificityforpathologicalproteinaggregates, and fMRI and FDG-PET reveal connectivity and metabolic deficits.DTI and emerging modalities enhance diagnostic precision by identifying microstructural, perfusion, and metabolic changes.Multimodal approaches, integrating imaging with CSF and blood- based biomarkers, achieve superior diagnostic accuracy, supporting timely interventions in preclinical and MCI stages.Technical advancements, such as high-field MRI, novel PETtracers,andAI-drivenanalysis,aretransformingthediagnosticlandscape.Despitechallenges in cost, accessibility, and standardization, ongoing innovations in portable imaging, biomarker integration, and global standardization promise to enhance the clinicalutilityofradiodiagnosis.ThissystematicreviewadheringtothePRISMAframework, underscores the transformative potential of radiodiagnostic modalities in early AD detection and emphasizes the need for equitable access and standardized protocols to ensure widespread clinical adoption.

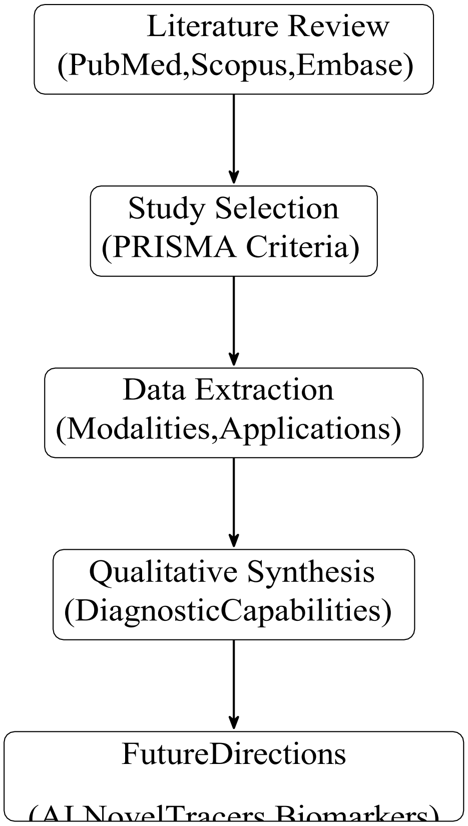

Figure 5: Flowchart of systematic review process and future directions in AD radiodiagnosis.

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