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DND Dementia and Neurocognitive Disorder

Original Article

The Usefulness of ^{18}F-FDG PET to Differentiate Subtypes of Dementia: The Systematic Review and Meta-Analysis

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Conflict of Interest
The authors have no financial conflicts of interest.

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ABSTRACT

Background and Purpose: Dementia subtypes, including Alzheimer's dementia (AD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD), pose diagnostic challenges. This review examines the effectiveness of [18]F-Fluorodeoxyglucose Positron Emission Tomography ([18]F-FDG PET) in differentiating these subtypes for precise treatment and management.
Methods: A systematic review following Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines was conducted using databases like PubMed and Embase to identify studies on the diagnostic utility of [18]F-FDG PET in dementia. The search included studies up to November 16, 2022, focusing on peer-reviewed journals and applying the gold-standard clinical diagnosis for dementia subtypes.
Results: From 12,815 articles, 14 were selected for final analysis. For AD versus FTD, the sensitivity was 0.96 (95% confidence interval [CI], 0.88–0.98) and specificity was 0.84 (95% CI, 0.70–0.92). In the case of AD versus DLB, 18F-FDG PET showed a sensitivity of 0.93 (95% CI 0.88-0.98) and specificity of 0.92 (95% CI, 0.70–0.92). Lastly, when differentiating AD from non-AD dementias, the sensitivity was 0.86 (95% CI, 0.80–0.91) and the specificity was 0.88 (95% CI, 0.80–0.91). The studies mostly used case-control designs with visual and quantitative assessments.
Conclusions: [18]F-FDG PET exhibits high sensitivity and specificity in differentiating dementia subtypes, particularly AD, FTD, and DLB. This method, while not a standalone diagnostic tool, significantly enhances diagnostic accuracy in uncertain cases, complementing clinical assessments and structural imaging.

Keywords: Fluorodeoxyglucose F18; Positron Emission Tomography Computed Tomography; Dementia; Meta-Analysis; Alzheimer's Disease; Frontotemporal Dementia; Lewy Body Disease

INTRODUCTION

Dementia is a syndrome characterized by a cognitive decline significantly interfering with activities of daily living and it is one of the leading causes of death.[1] Alzheimer's dementia (AD) is the most common subtype of dementia, accounting for a substantial portion of dementia cases in the elderly population. Alongside AD, dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD) are other notable forms, each contributing to the diverse spectrum of dementia pathologies. The ability to accurately differentiate between these subtypes of dementia is crucial for effective treatment and management.[2]

Imaging techniques play a pivotal role in dementia diagnosis. Structural brain imaging is conducted to differentiate space-occupying lesions such as tumors, hemorrhages, and significant vascular insults causing dementia.[3,4] In addition, imaging biomarkers are used to determine the neurodegeneration (N) status of the amyloid/tau/neurodegeneration (ATN) classification in AD spectrum disorder.[5,18]F-fluorodeoxyglucose positron emission tomography ([18]F-FDG PET) emerges as a significant diagnostic tool. [18]F-FDG PET uses a

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radioactive glucose compound to visualize the brain metabolism indicating the functional status. By analyzing patterns of glucose metabolism in the brain, [18]F-FDG PET is a constituent of the diagnosis of the three subtypes of FTD[6,7] and is also a biomarker for neurodegeneration status that is used for the ATN classification in AD.[5] The specific hypometabolism pattern of the [18]F-FDG PET helps to identify the characteristic signatures of AD, DLB, FTD, and other forms of dementia,[3,8,9] thus playing a vital role in the precise diagnosis and subsequent tailoring of therapeutic interventions.

In Korea, [18]F-FDG PET is one of the diagnostic methods for various neurodegenerative disorders in clinical settings. Recently, the Korean Dementia Association published clinical practice guidelines for dementia,[10] but it did not include the availability and utility of [18]F-FDG PET in the dementia assessment process. This systematic review aimed to specify the diagnostic utility of [18]F-FDG PET to differentiate subtypes of dementia in patients with cognitive decline.

METHODS

Search strategy

Databases including PubMed, Embase, KMbase, RISS, and the Cochrane Library were thoroughly searched following Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines to identify appropriate studies for the review. The following keywords were used: “Neurocognitive Disorders” or “Dementia” or “Alzheimer’s Disease” or “Aphasia, primary progressive” or “Frontotemporal lobar degeneration” or “Lewy Body Disease” and “Fluorodeoxyglucose F18”. Their MeSH terms and synonyms were also included to ensure thorough coverage and the inclusion of all relevant research papers. Articles included in the review were up to November 16, 2022.

Eligible criteria and study selection

The search was limited to papers published in peer-reviewed scientific journals. The articles were limited to those involving human studies and published in either English or Korean. In this review, the gold-standard diagnosis included was the clinical diagnosis of each dementia subtype. Two independent reviewers examined the literature and evaluated the articles for inclusion. In cases of disagreement between the reviewers, a discussion was held to settle the differences.

Data extraction and quality assessment

In the included studies, we extracted data for the study design, target disease (specific dementia subtype), patient sample size for each dementia subtype, assessment methods (visual vs. quantitative), reported measures of diagnostic accuracy, and the primary outcomes of each study. Considering that this review aimed to determine the diagnostic accuracy in differentiating between dementia subtypes, the sensitivity, and specificity for each condition were calculated using the data extracted from the included articles. All statistical analyses and forest plots were performed using Review Manager (RevMan) version 5.4 (Cochrane, London, UK) and STATA 15.1 (StataCorp, College Station, TX, USA). The risk of bias in the studies was assessed using the second version of the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2; University of Bristol, Bristol, UK).[11]

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RESULTS

Literature search results

The literature search resulted in 12,815 articles, from which 4,932 were selected for eligibility screening based solely on their titles and abstracts. Out of these, only 178 articles were considered for retrieval. Ultimately, 14 articles were included in the final selection (**Fig. 1**). The study information and outcomes are described in **Table 1.**[12-25]

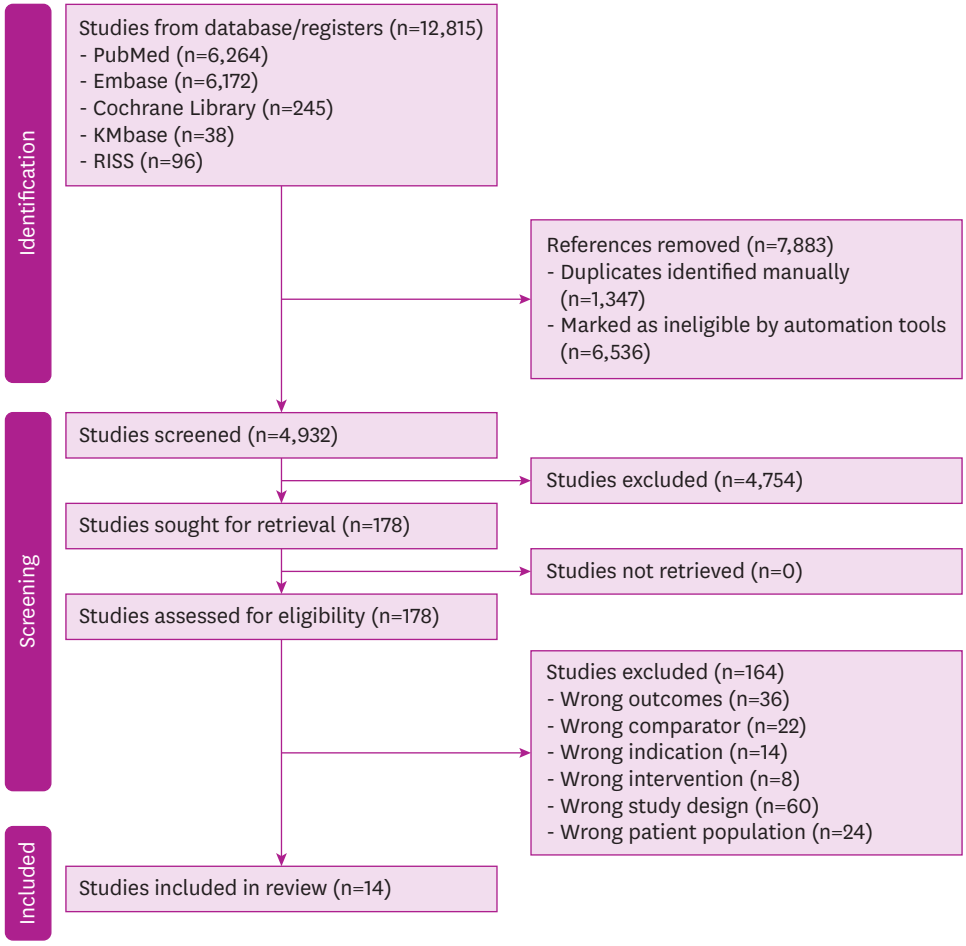

Fig. 1. PRISMA flowchart.
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Table 1. The characteristics and outcomes of the included studies

Study	Participants	Study information	Results
Rabinovici et al.[16] (2011)	62 AD, 45 FTD, 25 control	Visual assessment based on hypometabolism pattern and quantitative classification based on the ROI with the lowest Z score	1) Visual assessment - AD vs. FTD: Sn 75%–80%, Sp 83%–85%, PPV 87%–88%, NPV 70-74% 2) Quantitative classification - AD vs. FTD: Sn 73%, Sp 98%, PPV 98%, NPV 71%, AUC 0.910 (95% CI, 0.851–0.971)
Dukart et al.[12] (2011)	21 AD, 14 FTD, 13 control	Quantitative classification with: 1) whole brain voxel-based analysis and 2) disease-specific ROI-based analysis	1) Accuracy of whole brain-based analysis - AD vs. FTD: 82.9% 2) Accuracy of ROIs based analysis - AD vs. FTD: 80.0%

(continued to the next page)

Table 1. (Continued) The characteristics and outcomes of the included studies

Study	Participants	Study information	Results
Poljansky et al.[15] (2011)	16 AD, 16 FTD (9 bvFTD), 4 nfvPPA, 3 svPPA), 16 MCI	Visual assessment based on hypometabolism pattern (the severity ranged from 0 to 3) and quantitative classification with SPM analysis	1) Visual assessment - bvFTD vs. AD: Sn 89%, Sp 94% - FTD (bvFTD, svPPA, PPA) vs. AD: Sn 81%, Sp 94% - FTD vs. MCI: Sn 81%, Sp 64%
Panegyres et al.[23] (2009)	49 AD, 17 FTD, 6 DLB, 6 PPA, 11 depression	Visual assessment with 3D-SSP	1) AD vs. non-AD: Sn 78%, Sp 81%, PLR 4.11, NLR 0.27 2) Diagnostic accuracy of each dementia subtype - FTD: Sn 53% (29%–77%), Sp 95% (90%–100%) - LBD: Sn 83% (53%–100%), Sp 99% (97%–100%) - PPA: Sn 50% (10%–90%), Sp 100% (99%–100%)
Mosconi et al.[14] (2008)	110 controls, 114 MCI, 199 AD, 98 FTD, 27 DLB	Automated voxel-based comparison of disease-specific patterns (cortical and hippocampal pattern)	1) Analysis of cortical pattern - AD vs. Normal: Sn 99%, Sp 98% (98% accuracy) - AD vs. DLB: Sn 99%, Sp 71% (97% accuracy) - AD vs. FTD: Sn 99%, Sp 65% (97% accuracy) - DLB vs. FTD: Sn 71%, Sp 65% (68% accuracy) 2) analysis of hippocampal pattern - AD vs. Normal: Sn 98%, Sp 96% (97% accuracy) - AD vs. DLB: Sn 98%, Sp 75% (89% accuracy) - AD vs. FTD: Sn 98%, Sp 75% (89% accuracy) - DLB vs. FTD: Did not significantly discriminate 3) Cortical + hippocampal pattern - AD vs. DLB: Sn 98%, Sp 100% (99% accuracy) - AD vs. FTD: Sn 98%, Sp 94% (97% accuracy)
Jagust et al.[20] (2007)	(pathology confirmed) 25 AD, 19 non-AD	Visual assessment based on hypometabolism pattern	- AD vs. non-AD: Sn 84%, Sp 74%, PPV 81%, NPV 78%
Foster et al.[13] (2007)	(pathology confirmed) 31 AD, 14 FTD	Visual assessment of transaxial images and SSP images	1) Transaxial ^{18}F-FDG PET - Mean PPV for FTD/NPV for AD 68% - Mean NPV for FTD/PPV for AD 91% - PLR for FTD 14.8, NLR for FTD 0.4 - PLR for AD 2.5, NLR for AD 0.2 2) SSP ^{18}F-FDG PET - Mean PPV for FTD/NPV for AD 93% - Mean NPV for FTD/PPV for AD 89% - PLR for FTD 36.5, NLR for FTD 0.3 - PLR for AD 3.5, NLR for AD 0.03
Perini et al.[21] (2021)	177 MCI, 100 dementia with uncertain diagnosis (43 AD, 24 FTD, 14 DLB, 7 others, 12 unspecified dementia)	Visual assessment with standardized uptake value ratios based on ROIs and voxel-wise Z-score SSP analysis	- AD vs. non-AD: Sn 76%, SP 95%, ACC 86%, PLR 13.7, NLR 0.2 - FTD vs. non-FTD: Sn 82%, SP 90%, ACC 88%, PLR 8.5, NLR 0.2 - DLB vs. non-DLB: Sn 75%, SP 95%, ACC 92%, PLR 15.6, NLR 0.3
Vijverberg et al.[25] (2016)	27 bvFTD, 84 non-bvFTD	Visual assessment	- bvFTD vs. non-bvFTD: Sn 70%, Sp 93%, PPV 76%, NPV 91%
Taswell et al.[24] (2015)	24 AD, 19 logopenic PPA, 16 nfvPPA, 13 svPPA, 14 CBS	Visual assessment with 3D-SSP technique	- AD vs. non-AD pathology: PPV 0.95, NPV 0.42, PLR 2.71, NLR 0.19
O'Brien et al.[18] (2014)	38 AD, 30 DLB, 30 controls	Visual assessment based on hypometabolism pattern and quantitative classification with SPM analysis	1) Visual assessment - AD vs. DLB: Sn 74%, Sp 70%, AUC 0.799 ± 0.059 2) Quantitative classification - AD vs. DLB: ROI medial occipital/MTL, AUC 0.855 ± 0.055
Spehl et al.[19] (2015)	15 AD, 6 PCA, 12 DLB	Visual assessment based on hypometabolism pattern and quantitative classification with SPM analysis	1) Visual assessment: overall accuracy 83% - PCA: Sn 83%, Sp 85% - DLB: Sn 83%, Sp 81% 2) Quantitative classification: overall accuracy 73% - PCA: Sn 83%, Sp 93%, AUC 0.91 - DLB: Sn 75%, Sp 86%, AUC 0.85 - AD: Sn 67%, Sp 78%, AUC 0.77
Tripathi et al.[22] (2014)	61 AD, 18 FTD, 9 DLB, 13 others (CJD, VD, PCA, mixed dementia)	Visual assessment	- AD vs. non-AD: Sn 93.4%, Sp 87.5% - FTD vs. non-FTD: Sn 88.8%, Sp 100% - DLB vs. non-DLB: Sn 66.6%, Sp 98.3%
Lim et al.[17] (2009)	10 AD, 14 DLB	Visual assessment based on hypometabolism pattern	- DLB vs. AD: Sn 83%, Sp 93%

AD: Alzheimer's dementia, FTD: frontotemporal dementia, ROI: region of interest, Sn: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value, AUC: area under curve, CI: confidence interval, bvFTD: behavioral variant frontotemporal dementia, nfvPPA: nonfluent variant primary progressive aphasia, svPPA: semantic variant primary progressive aphasia, MCI: mild cognitive impairment, SPM: statistical parametric mapping, PPA: primary progressive aphasia, DLB: dementia with Lewy bodies, 3D: 3-dimensional, SSP: stereotactic surface projection, PLR: positive-likelihood ratio, NLR: negative-likelihood ratio, CBS: corticobasal syndrome, PCA: posterior cortical atrophy, CJD: Creutzfeldt-Jakob disease, VD: vascular dementia.

Quality assessment

The risk of bias during patient selection was notably high in 1 of the 14, unclear in 9, and low in 4 articles. Index tests in 3 studies exhibited unclear risk, while the remainder were deemed low risk. For the reference standard, a single study had a high risk of bias, 2 had an unclear risk, and the remaining articles exhibited a low risk. The risk was consistently low in the flow and timing domain across all articles. Regarding applicability concerns, only one study in the patient selection domain showed an unclear risk of bias, whereas the others were classified as low risk. All articles exhibited a low risk of bias in the index test and reference standard domains (**Fig. 2**). **Fig. 3** illustrates the summary of bias risks and concerns regarding the applicability of each article.

Meta-analysis

A meta-analysis was conducted to aggregate the sensitivity and specificity data for diagnostic accuracy. To illustrate the diagnostic accuracy of [18]F-FDG PET, forest plots were generated. In cases where an article provided multiple sets of sensitivity and/or specificity data for various conditions (such as comparing different dementia subtypes) or used distinct assessment

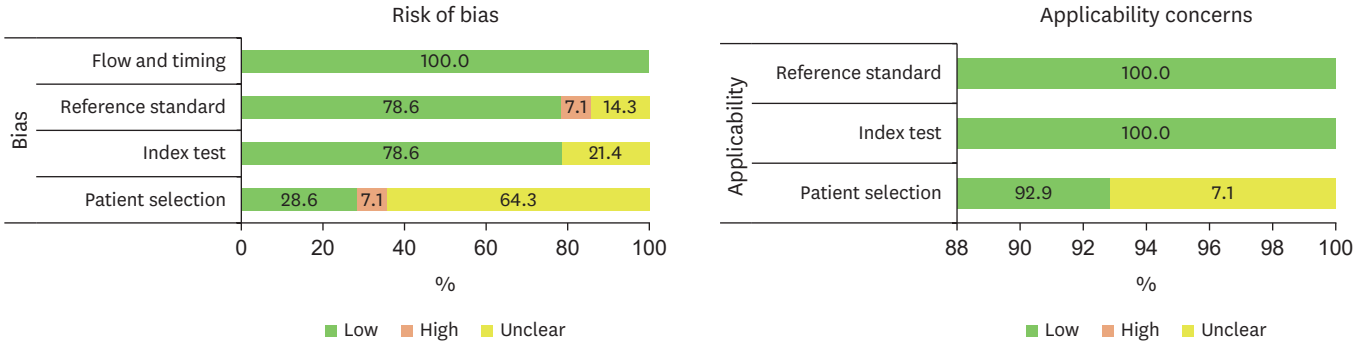

Fig. 2. Graph for risk of bias and applicability concerns.

Study	Risk of Bias				Applicability concern		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Rabinovici et al.[16] (2011)	?	+	+	+	+	+	+
Dukart et al.[12] (2011)	X	+	?	+	?	+	+
Poljansky et al.[15] (2011)	?	+	+	+	+	+	+
Panegyres et al.[23] (2009)	?	?	+	+	+	+	+
Mosconi et al.[14] (2008)	?	+	+	+	+	+	+
Jagust et al.[20] (2007)	?	+	+	+	+	+	+
Foster et al.[13] (2007)	?	+	+	+	+	+	+
Perini et al.[21] (2021)	?	?	X	+	+	+	+
Vijverberg et al.[25] (2016)	+	+	+	+	+	+	+
Taswell et al.[24] (2015)	?	+	+	+	+	+	+
O'Brien et al.[18] (2014)	+	+	+	+	+	+	+
Spehl et al.[19] (2015)	?	+	+	+	+	+	+
Tripathi et al.[22] (2014)	+	?	?	+	+	+	+
Lim et al.[17] (2009)	+	+	+	+	+	+	+

Judgement: X High; + Low; ? Unclear

Fig. 3. Summary of risk of bias and applicability concerns.

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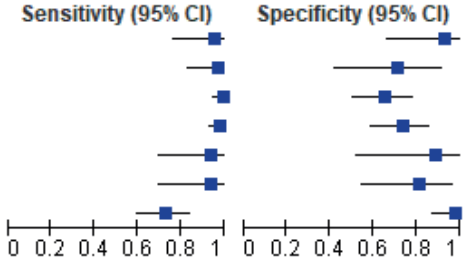
methods or targeted different patients groups, these were recorded as duplicates of the original study reference, marked with the letters 'a' and 'b.'

In differentiating AD from FTD, as shown in **Fig. 4A**, 7 results showed that [18]F-FDG PET had a sensitivity of 0.96 (95% confidence interval [CI], 0.88–0.98) and specificity of 0.84 (95% CI, 0.70–0.92).[12,16] All studies included in the analysis were case-control studies. Qualitative analysis used visual assessment, and facilitated reading by providing transaxial and stereotactic surface projection (SSP) images to the interpreters. The FTD group included behavioral variant type, non-fluent variant of primary progressive aphasia, and semantic dementia. FTD typically showed hypometabolism in the frontal lobe, anterior cingulate cortex, and temporal regions, whereas AD showed hypometabolism in the temporal and parietal lobes, and posterior cingulate cortex.

When gathering evidence from five results of four studies, [18]F-FDG PET showed a sensitivity of 0.93 (95% CI, 0.88–0.98) and specificity of 0.92 (95% CI, 0.70–0.92) in differentiating between AD and DLB (**Fig. 4B**).[14,17,19] All the included studies were case-control designs.

A

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dukart 2011	20	1	1	13	0.95 [0.76, 1.00]	0.93 [0.66, 1.00]
Foster 2007	30	4	1	10	0.97 [0.83, 1.00]	0.71 [0.42, 0.92]
Mosconi 2008a	99	17	1	32	0.99 [0.95, 1.00]	0.65 [0.50, 0.78]
Mosconi 2008b	98	13	2	36	0.98 [0.93, 1.00]	0.73 [0.59, 0.85]
Poljansky 2011a	15	1	1	8	0.94 [0.70, 1.00]	0.89 [0.52, 1.00]
Poljansky 2011b	15	3	1	13	0.94 [0.70, 1.00]	0.81 [0.54, 0.96]
Rabinovici 2011	43	1	16	40	0.73 [0.60, 0.84]	0.98 [0.87, 1.00]

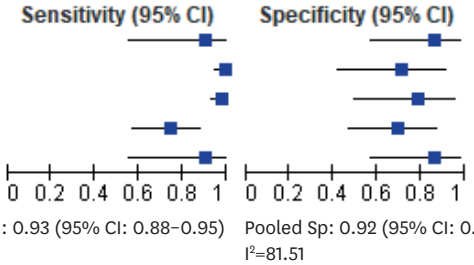


Pooled Sn: 0.96 (95% CI: 0.88–0.98)
I^2=87.70

Pooled Sp: 0.84 (95% CI: 0.70–0.92)
I^2 = 66.18

B

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lim 2009	9	2	1	12	0.90 [0.55, 1.00]	0.86 [0.57, 0.98]
Mosconi 2008	99	4	1	10	0.99 [0.95, 1.00]	0.71 [0.42, 0.92]
Mosconi 2008b	98	3	2	11	0.98 [0.93, 1.00]	0.79 [0.49, 0.95]
O'Brien 2014	26	7	9	16	0.74 [0.57, 0.88]	0.70 [0.47, 0.87]
Spehl 2015	9	2	1	12	0.90 [0.55, 1.00]	0.86 [0.57, 0.98]

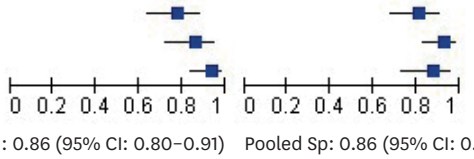


Pooled Sn: 0.93 (95% CI: 0.88–0.95)
I^2=82.47

Pooled Sp: 0.92 (95% CI: 0.87–0.95)
I^2=81.51

C

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jagust 2007	21	5	4	14	0.84 [0.64, 0.95]	0.74 [0.49, 0.91]
Panegyres 2009	38	10	11	43	0.78 [0.63, 0.88]	0.81 [0.68, 0.91]
Perini 2021	37	4	6	53	0.86 [0.72, 0.95]	0.93 [0.83, 0.98]
Tripathi 2014	57	5	4	35	0.93 [0.84, 0.98]	0.88 [0.73, 0.96]



Pooled Sn: 0.86 (95% CI: 0.80–0.91)
I^2=50.00

Pooled Sp: 0.86 (95% CI: 0.80–0.91)
I^2=47.90

Fig. 4. Forest plots of sensitivity and specificity of the [18]F-FDG PET for differentiating (A) AD from FTD, (B) AD from DLB, and (C) AD from non-AD.
[18]F-FDG PET: [18]F-fluorodeoxyglucose positron emission tomography, AD: Alzheimer's dementia, FTD: frontotemporal dementia, DLB: dementia with Lewy bodies, TP: true positive, FP: false positive, FN: false negative, TN: true negative, CI: confidence interval, Sn: sensitivity, Sp: specificity.

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[18]F-FDG PET analysis involved visual assessment and quantitative analysis comparing voxel-level in regions of interest (ROI) using the statistical parametric mapping program. Patients with AD showed hypometabolism in the parietal lobe, temporal lobe (including the hippocampus), and some parts of the frontal lobe, while those with DLB showed hypometabolism primarily in the parieto-occipital cortex with preservation of brain metabolism in the posterior cingulate cortex.

When synthesizing results of four studies in differentiating AD from non-AD, [18]F-FDG PET demonstrated a sensitivity of 0.86 (95% CI, 0.80–0.91) and specificity of 0.88 (95% CI, 0.80–0.91) (**Fig. 4C**).[20-23] Taswell et al.[24] showed that in a cohort consisting of primary progressive aphasia, corticobasal degeneration, and AD, the use of [18]F-FDG PET for differentiating AD demonstrated a positive predictive value of 0.95 and a negative predictive value of 0.42. However, this study was excluded from meta-analysis due to the lack of specific sensitivity and specificity data. Among the included studies, four were case-control studies, and one was a cohort study. All studies were conducted using qualitative analysis with visual assessment, and quantitative results were also provided. The non-AD group included various conditions like FTD, DLB, depression, unspecified dementia, Creutzfeldt-Jakob disease, and mixed dementia, with each study having different subjects.

Three studies that differentiated FTD from non-FTD were found, all using qualitative analysis through visual assessment. Two studies, by Perini et al. [21] and Tripathi et al.,[22] were case-control studies, and the study by Vijverberg et al.[25] was a cohort study. In the study by Perini et al.,[21] 100 patients with uncertain dementia subtype diagnosis were classified into FTD, AD, DLB, and other types of dementia using [18]F-FDG PET. The diagnostic assessment with [18]F-FDG PET at the initial stage showed a sensitivity of 0.82 and a specificity of 0.90. Similar results were obtained when the final diagnosis was based on data collected about 3.8 years later, with a sensitivity of 0.83 and a specificity of 0.89. Tripathi et al.[22] used [18]F-FDG PET to differentiate FTD from Creutzfeldt-Jakob disease, vascular dementia, mixed dementia, posterior cortical atrophy, and AD, showing a sensitivity of 0.89 and specificity of 1.00. Vijverberg et al.[25] analyzed behavioral variant FTD differentiation from vascular cognitive impairment, other dementias, AD, DLB, and major psychiatric disorders using [18]F-FDG PET and showed a sensitivity of 0.70 and a specificity of 0.93.

DISCUSSION

This meta-analysis and review showed that the [18]F-FDG PET had a sensitivity of 0.96 and a specificity of 0.84 in differentiating AD and FTD, a sensitivity of 0.93 and a specificity of 0.92 in differentiating AD and DLB, and a sensitivity of 0.86 and a specificity of 0.86 in differentiating AD and non-AD. Most studies were case-control designs and adopted visual assessment and/or quantitative analysis.

Previous studies demonstrated that when adopting [18]F-FDG PET method over the clinical diagnosis or structural imaging, the diagnostic accuracy can be increased.[12,20,21,25] The National Institute for Health and Care Excellence guidelines of dementia assessment,[26] the Canadian Consensus Conferences on the Diagnosis and Treatment of Dementia,[27] and the European Federation of the Neurological Societies (EFNS) guideline[3] for the use of neuroimaging in dementia also recommend [18]F-FDG PET for cases in which the diagnosis is still uncertain following clinical evaluation and structural magnetic resonance imaging (MRI)

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analysis. Some guidelines also warned that diagnosis solely based on the findings of brain imaging should be avoided.[26,28] In addition to its role in differentiating dementia subtypes, the EFNS guideline indicated that normal findings from an [18]F-FDG PET scan reduce the likelihood of a neurodegenerative diagnosis when there is suspicion of dementia.[3]

The analysis of [18]F-FDG PET is usually conducted through visual assessment and is based on disease-specific hypometabolism patterns. In this meta-analysis, studies with both visual interpretation and quantitative assessment were included. For the visual interpretation, the scoring system was adopted according to the severity of hypometabolism in specific brain regions, or the quantitative statistical mapping approach was used.[29] In statistical mapping, the initially reconstructed images undergo realignment through stereotactic transformation for anatomic standardization. The anatomically standardized images are compared with the age-matched cognitively normal subjects. The deviations between the individual scan and the normal database are displayed as a z-score map. To further reduce the remaining anatomical differences among subjects and to lessen the impact of cortical atrophy on this comparison, a 3-dimensional SSP algorithm can be used to extract and reduce.[30] Using a quantitative statistical mapping method can enhance the likelihood of a positive diagnostic outcome [29,30] and the studies featured in this review also demonstrated comparable findings.[13,16,18,19]

With the commercial availability of amyloid PET, it has become easier to determine if a patient with dementia is on the Alzheimer's spectrum. [31,32] However, for FTD diagnosis, there is no specific method in the clinical setting for directly visualizing FTD pathology. The components of the diagnostic criteria include brain atrophy observed in structural imaging, hypometabolism in [18]F-FDG PET scans, or perfusion defects in brain SPECT imaging, particularly in areas of the brain specific to FTD subtypes. [6,7] Certainly, compared to molecular imaging targeting fundamental neuropathologies like amyloid-beta or tau, [18]F-FDG PET and MRI assess secondary neurodegenerative changes, reflecting the characteristic topographic patterns of a specific dementia subtypes. Thus these methods might not accurately predict the actual pathology in cases where the disease manifests in atypical patterns, such as in frontal-type AD or early-onset AD. [16,33] Considering [18]F-FDG PET's greater specificity relative to amyloid imaging, which is more sensitive at thresholds aimed at maximizing classification accuracy, employing [18]F-FDG PET for distinguishing AD from FTD can be beneficial.[16] To differentiate DLB from AD, various functional imaging modalities, such as [18]F-FDG PET and [123]I-β-CIT SPECT, are known to be helpful.[17,34,35] The cingulate island sign observed in [18]F-FDG PET is a representative supportive biomarker for DLB.[34,35]

When choosing an appropriate diagnostic tool from the various methods available for dementia diagnosis, we should consider the complex clinical profile, environment, and accessibility for each patient. The most common cause of dementia, AD, is characterized by insidiously progressive cognitive impairment, especially in the decline of episodic memory in the elderly.[1] However, when a patient presents with atypical symptoms such as early onset, cognitive impairments in domains other than memory, or fluctuating or rapidly progressive symptoms, etiologies other than AD should be considered. Each subtype of dementia has a different response to various medications, as well as distinct clinical courses, prognoses, and mortality rates.[36] Additionally, unclear diagnoses can result in inadequate treatment. A previous study demonstrated that donepezil was linked to a worsening of behavioral symptoms, including disinhibition and impulsivity, in FTD cases.[37] Hence, an accurate diagnosis of specific dementia subtype is crucial.

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Amyloid-PET is a representative neuroimaging technique to detect amyloid plaques, which are key neuropathological features in Alzheimer's disease.[38] In patients with confirmed Alzheimer's disease who underwent an autopsy within one year of PET imaging, Amyloid-PET revealed a high sensitivity (96%) and a specificity (100%).[39] The diagnostic accuracy of amyloid PET is higher than that of [18]F-FDG-PET.

Considering the high sensitivity in identifying amyloid plaques, a negative scan of amyloid-PET can also be used to reliably rule out Alzheimer's disease as the underlying cause in patients with atypical clinical presentations such as abnormal behavior or primary progressive aphasia.[31] However, despite its higher sensitivity and specificity for detecting Alzheimer's pathology, several factors must be considered. The prevalence of amyloid pathology among those with normal cognition increases with age; approximately 30% of cognitively unimpaired individuals aged 80 show amyloid positivity.[40] Moreover, mixed pathology is observed in 10%–74% of community-based cohorts.[41] These findings suggest that while amyloid PET exhibits higher sensitivity and specificity in detecting amyloid pathology, other complementary diagnostic tools, such as [18]F-FDG-PET, may be needed in complex cases.[31]

Regarding the risks associated with the [18]F-FDG PET, recent multi-institutional research in Korea revealed that the effective radiation dose from a whole-body [18]F-FDG PET scan for a 70 kg adult is 10.93 ± 3.14 mSv.[42] Furthermore, this dose for [18]F-FDG PET scans that only image the brain is reduced, as compared to torso PET, resulting in an even lower effective radiation dose. The American Association of Physicists in Medicine has stated that the radiation exposure level from a single medical imaging procedure is considered very low or negligible if it is below 50 mSv.[43] When using [18]F-FDG PET in clinical practice, several important factors must be considered, such as the availability of referral clinics capable of conducting [18]F-FDG PET studies and the cost-effectiveness of the procedure. In Korea, the National Evidence-based Healthcare Collaborating Agency (NECA) conducted an email survey (December 11–19, 2014) to evaluate awareness and attitudes toward 'dementia diagnostic tests' and to determine the preference for [18]F-FDG PET brain imaging in the early diagnosis of dementia.[44] When asked about undergoing a test for early dementia diagnosis, which includes consultation with a specialist and a neurological examination, 54.6% of the respondents indicated they would. However, when queried about their willingness to undergo [18]F-FDG PET, considering its sensitivity and specificity for early dementia diagnosis and the average cost, only 31.2% (312/1,000) responded affirmatively, while 68.8% (688/1,000) declined. The most frequent reason for refusal was the cost burden. Currently, in Korea, [18]F-FDG PET is not covered by insurance for purposes other than cancer. Given that approximately 67% of respondents were open to detailed imaging tests but only 31.2% consented to [18]F-FDG PET, with the majority citing cost as a concern, this indicates that financial implications play a significant role in the patient's values and preferences.

This review has several limitations. First, the search for included studies was conducted up to November 16, 2022. However, the most recent article included in our review was published in 2021.[21] Therefore, it is possible that the latest papers, published after this date, may not have been included. Second, various articles focusing on the diagnostic utility of FDG-PET might have been excluded if they deviated from the objective of this review, which is the differentiation of dementia subtypes. This is because our review did not aim to address the potential conversion from mild cognitive impairment (MCI) to dementia, or the differentiation of neurodegenerative disorders from normal status.

DND Dementia and Neurocognitive Disorder

As a clinical physician, it is essential to understand the expected diagnostic accuracy and identify the appropriate circumstances in which [18]F-FDG PET might be considered. To facilitate the clinical application of [18]F-FDG PET, the Korean version of the guideline for the use of [18]F-FDG PET for differential diagnosis of dementia subtypes is provided as **Supplementary Data 1**. This review demonstrates that the application of [18]F-FDG PET in dementia assessment can yield high sensitivity and specificity in differentiating between dementia subtypes. While [18]F-FDG PET cannot solely replace a comprehensive clinical assessment for diagnosing dementia subtypes, it serves as a supplementary method to enhance diagnostic accuracy, particularly when the diagnosis of dementia is uncertain.

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SUPPLEMENTARY MATERIAL

Supplementary Data 1

Korean version of systematic review

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