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■ ORIGINAL ARTICLE ■

Efficacy of the Phosphorylated tau 181 in Differential Diagnosis of the Alzheimer's Disease - A Systematic Review and Meta-Analysis

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Background: The purpose of this study was to evaluate the value of phosphorylated tau with epitopes threonine 181(p-tau$_{181}$) in cerebrospinal fluid (CSF) for the differential diagnosis of Alzheimer's disease typed dementia from other type of dementia. **Methods:** A systematic literature search was performed to identify studies on p-tau$_{181}$. Two evaluators independently evaluated the quality of the ten studies using the Scottish Intercollegiate Guidelines Network (SIGN) tool. The literature review covered from October 27, 1946 to October 22, 2013, and eight domestic databases including KoreaMed and international databases including Ovid-MEDLINE, EMBASE, and Cochrane Library were used. Tau concentrations were compared to healthy controls and to subjects with Alzheimer's disease (AD) using random effect meta-analysis. Outcome measures were Cohen's delta, sensitivity and specificity. **Results:** Finally, 8 studies (8 diagnostic evaluation studies) were identified to evaluate CSF p-tau$_{181}$. The effectiveness of this test was evaluated based on diagnostic accuracy. The diagnostic accuracy for identifying AD by ELISA was high which revealed pooled sensitivity as 0.843 (95% CI 0.818-0.867), pooled specificity as 0.799(95% CI 0.768-0.828) and summary receiver operating characteristic area under the curve 0.9082 ± 0.0236. **Conclusions:** CSF p-tau$_{181}$ concentrations in other type of dementia are intermediate between controls and AD patients. Overlap between both controls and AD patients results in insufficient diagnostic accuracy, and the development of more specific biomarkers for these disorders is needed.

Key Words: *Alzheimer's disease, Cerebrospinal fluid, Tau protein, Meta-analysis, Systemic review*

INTRODUCTION

Dementia is now becoming huge social problem and Alzheimer's disease (AD) is the most common type of dementia among various types of it [1]. So, suitable strategies for diagnosis, treatment and prevention for AD are very important. Recent revised diagnostic criteria for AD by the National Institute on Aging and the Alzheimer Association broaden the spectrum of AD from dementia phase to preclinical and pre-dementia phase [2]. After successive failures of large scale clinical therapeutic trials focused on AD dementia, many researchers insisted on moving to early stage of disease such as preclinical or pre-dementia stage for the initiation of AD therapeutics [3, 4]. To perform this, the early diagnosis of AD is essential and the biomarkers play a great role in those fields [5]. AD biomarkers might be grouped into two categories

based on the biologic viewpoint. They are biomarkers of amyloid-beta (Aβ) depositions measured using cerebrospinal (CSF) Aβ or amyloid PET imaging, and neuronal degeneration measured using CSF tau, 18 fluorodeoxyglucose (FDG) PET or structural MRI [6]. Among these various biomarkers, those based on CSF reflect essential neuropathology characteristics of AD such as amyloid plaque and neurofibrillary tangles and [7] and these pathologic changes precede clinical onset of dementia by more than 20 years. Therefore, CSF biomarkers are appropriate candidate for very early diagnosis of AD. Because tau pathology such as neurofibrillary tangle was found in the entorhinal cortex of early stage of AD patient [8], a tau protein regarded as promising candidate for biomarker that could be used in clinical practice. And most studies suggested that phosphorylated tau (p-tau) had much more specificity than total tau (t-tau) for the diagnosis of AD. Recent immunoassays can measure the phosphorylated epitope of threonine 181 (p-tau_{181}), serine 199 (p-tau_{199}), threonine 231 (p-tau_{231}) or combination of them. Among these subtypes of p-tau, p-tau_{181} is approved for clinical practice in Korea and different tau epitopes had similar values, showing no significant difference among them [9]. To evaluate the clinical value of p-tau_{181} in CSF for the differential diagnosis of AD, we aimed to integrate studies which have studied p-tau_{181}. We are to evaluate the difference between AD versus other dementia, AD versus subject with normal cognition and amnestic mild cognitive impairment (MCI) versus non-amnestic MCI using systemic review of literature and meta- analysis.

METHODS

Search strategy

We conducted a systematic review on the eight Korean database including KoreaMed, and electronic databases MEDLINE, EMBASE, and Cochrane Library according to the reporting guidelines of the Arbitration Act Handbook (Hoggins and Green) as proposed by the Cochrane Union (Cochrane collaboration) and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) group. Reviewers comprised two methodological experts, two experts in laboratory medicine, two neurologists, and one neurological surgeon. Six meetings were held to (i) establish selection criteria, (ii) review studies selected for inclusion, (iii) overview data extraction, (iv) refine and validate the conclusions of the study.

Keywords "(Alzheimer Disease.mp. OR exp Alzheimer Disease/) AND (Cerebrospinal Fluid.mp. OR exp Cerebrospinal Fluid/) AND (pTau181.mp. OR phosphorylated tau 181.mp.) were used to search for the exposure and outcomes of interest, as well as confine our search to mild cognitive impairment and Alzheimer's disease type dementia studies. Studies were limited to those published after 2004 owing to the lack of well-developed phosphorylated tau assays before this time. The first stage involved reviewing only the title and abstract of each article and the second stage involved reviewing the full text. Then, we made Patients-Intervention-Comparators-Outcomes (PICO) and search strategy.

Table 1. Ovid-MEDLINE and EMBASE search strategy

PICO	No	Search term	Searched literature (n)	
			MEDLINE	EMBASE
Patients	1	dementia.mp. or Dementia/	84,165	115,778
	2	Alzheimer Disease/ or alzheimer.mp.	73,731	123,948
	3	cognitive impairment.mp. or Mild Cognitive Impairment	25,886	39,463
	4	1 or 2 or 3	147,525	217,553
Index test	5	(phospho$ adj2 181).mp.	97	103
	6	P tau.mp.	474	623
	7	$tau.mp.	24,805	26,745
	8	5 or 6 or 7	24,851	26,795
	9	cerebrospinal fluid.mp. or Cerebrospinal Fluid	75,623	135,751
	10	CSF.mp. or Cerebrospinal Fluid	85,509	138,707
	11	([Lumbar or spinal] and puncture).mp.	9,491	17,424
	12	9 or 10 or 11	128,395	189,995
	13	8 and 12	2,716	4,773
P+I	14	4 and 13	2,081	3,982
	15	ANIMALS/	5,486,090	1,890,932
	16	HUMANS/	13,631,608	14,862,188
	17	15 and 16	1,528,202	482,645
	18	16 not 17	3,957,888	1,408,287
	19	14 not 18	2,006	3,972
	20	elisa.mp. or Enzyme-Linked Immunosorbent Assay	181,268	238,511
	21	Immunoassay.mp. or Immunoassay	56,681	101,986
	22	Pib and (PET or positron emission tomography.mp.)	477	1,023
	23	(biopsy or autopsy).mp.	393,696	693,753
	24	Innotest or Biosource or AlzBio	120	575
	25	20 or 21 or 22 or 23 or 24	800,265	1,206,161
	26	19 and 25	496	957
Total			496	957

PICO, Patients- Intervention- Comparators-Outcomes.

Inclusion and exclusion criteria

The searches included in Korean and English. It had to fulfill criteria for study quality: a prospective cohort (including case-cohort or nested case-control designs); measurement of the relevant p-tau; a study reporting the relative risk or equivalent effect estimates for incident AD, and/or mean differences in cognitive decline for studies of that outcome should have at least follow-up duration; and be adjusted for age at a minimum.

We excluded animal or preclinical studies and non-systematic reviews, editorial, letter, comment, opinion pieces, review, congress or conference material, guideline, note, news article, and abstract.

Study selection

After the initial keyword search, there were 496 results from MEDLINE, 957 from EMBASE, and 0 from domestic database for a total of 1,453 studies. There were also 1 manual-searched domestic and 49 foreign studies. We excluded duplicated documents, those about animal study or preclinical studies which was not written in English or Korean. As a result, 203 studies were identified for the further consideration. After two investigators independently reviewed the remaining articles and performed the first stage of selection. Finally, eight studies that met all of our inclusion criteria remained (Fig. 1).

Level of evidence in the literature

Studies were evaluated using the Methodology Checklist

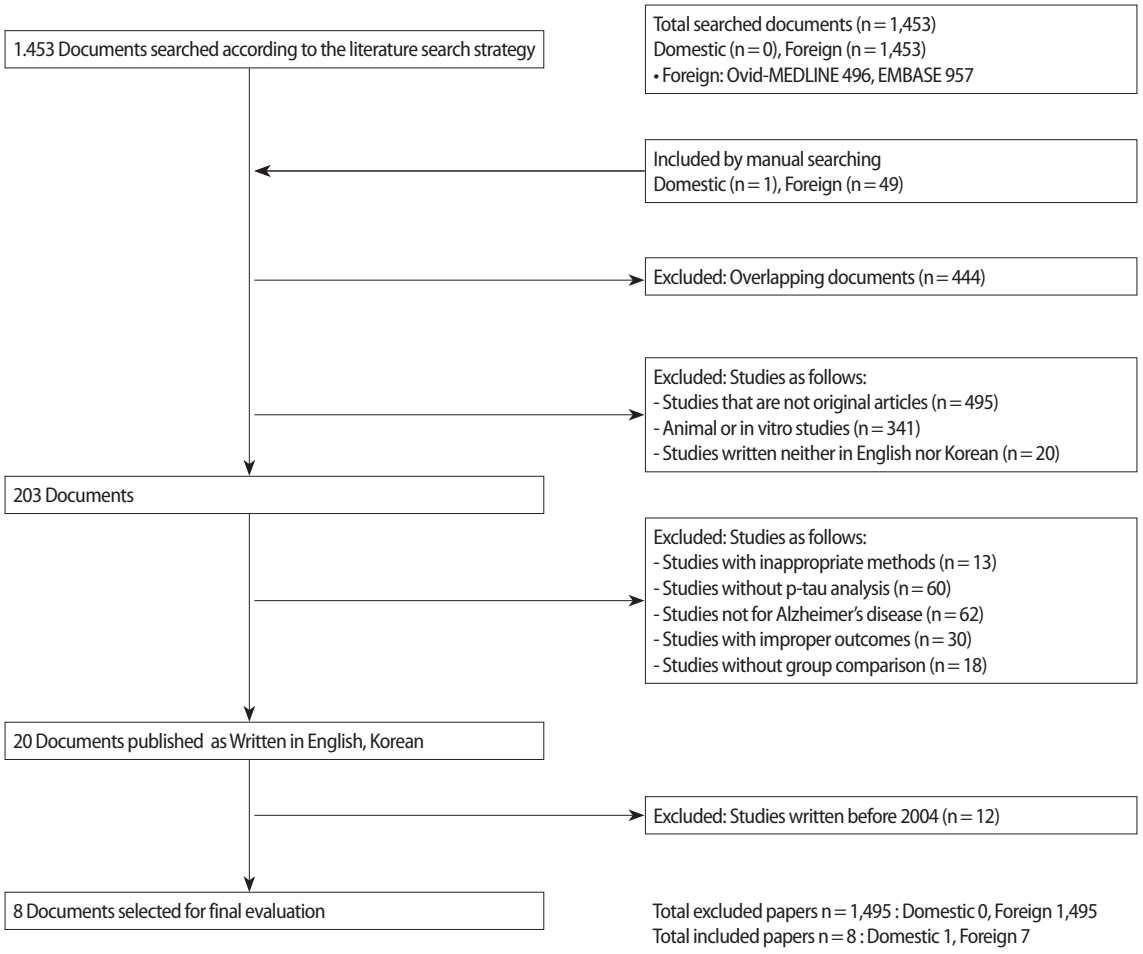


Fig. 1. Flow diagram processed on the article selection.

Table 2. Levels of evidence (SIGN 50)

1++	• High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	• Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	• Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	• High quality systematic reviews of case control or cohort or studies • High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	• Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	• Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	• Non-analytic studies, e.g. case reports, case series
4	• Expert opinion

SIGN, Scottish Intercollegate Guidelines Network tool; RCT, a randomized controlled trial.

Table 3. Grades of recommendations (Health Insurance Review Agency 2005)

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

RCT, a randomized controlled trial.

for Randomized Controlled Trials (RCTs) of the Scottish Intercollegiate Guidelines Network (SIGN). Two investigators independently, together with the study type (Table 2), decided the Level of Evidence (1++ to 1−, 2++ to 2−, 3, 4) that led to the pragmatic Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Recommendation (A–D) (Table 3).

Data extraction

The variables were extracted from each study by two independent investigators. They were consisted of diagnosis; year of publication; study design; name of cohort, exposures measured, and variable coding methods; outcomes measured; length of follow-up; sample size; demographics (mean age at baseline, sex, and ethnicity); effect measures, respective P values and confidence intervals, and/or standard errors; number of cases in each group; and covariates used in modeling; country of study population. Selection and categorization were performed in other researchers. The data were then categorized according to the type of data, study characteristics, and the reliability of the techniques employed.

Final extraction of data from validated primary sources was performed by two evaluators.

Statistical anaylyses

Chi-square (χ^2) analysis was used to compare numerical values of β-amyloid levels between different disease categories. Confidence intervals were determined using the means and standard deviations reported in each document. Meta-analysis was performed to assess the overall diagnostic accuracy of the pooled reports based on the fixed effects model. In addition, a funnel plot was used to address publication bias and the I2 test for heterogeneity of studies was performed. SPSS (Statistical Package for the Social Sciences) 21.0 (SPSS/IBM Inc, New York) was used to recalculate the reported the χ^2 values. Revman 5.0 MetaDiSc 1.4 version (Hospital Universtario Ramony Cajal, Madrid, Spain) was subsequently used for meta-analysis of the entire dataset.

RESULTS

Included and excluded studies

The 1,503 studies including 50 with manual search were identified. Among them, 444 studies were overlapping documents and a total of 856 were excluded according to the exclusion criteria described above. On top of that, studies with inappropriate method (n = 13), those without p-tau analysis

Table 4. Documents selected for evaluation of phosphorylated tau p181

First author	Publication year	Subjects (n)	Index test	Subgroup	Mean	SD	N	TP	FP	FN	TN	Level of evidence
Dumurgier	2013	AD (515)	O (> 54-65)	AD	92.1	41.9	515	133	20	22	163	
				Other	49.6	28	365	239	29	53	99	++
								130	44	27	139	
Park	2013	AD (17)	O (> 54)	AD	80	31	17					
				Other	38.6	22.6	9					++
				Control	46.5	9	12	14	1	3	11	
Ravaglia	2008	AD (51)	O (> 35.5)	AD	63.5	40.3	51					
				Other	18.8	6.7	19	32	19	5	14	++
				Control	24.8	5.9	36	32	19	0	36	
Reijn	2007	AD (74)	O (> 67)	AD	98	25	69					
				Other	45	13	26	66	7	3	48	++
				Control	46	10	55	63	9	6	46	
Schoonenboom	2004	AD (47)	O (> 54)	AD	79	130.5	47					
				Other	41	61.5	28	40	5	7	23	++
				Control	35	34.5	21	40	5	7	16	
Le Bastard	2013	AD (51)	O (> 50)	AD	66	50	51					
				Other	41	19.5	95	39	19	12	76	+
				Control	40	57	95	39	21	12	74	
Herukka	2008	MCI (21)	O (> 70)	a MCI	100	25	13					+
				na MCI	70	27	8	7	6	1	7	
Kapaki	2007	AD (67)	O (> 61)	AD	72	19.8	67					
				Other	34.8	13.35	18	59	2	8	16	+
				Control	45.1	7.9	72	50	5	17	67	
Lewczuk	2007	AD (22)	O (-)	a MCI	48.6	23.65	106					-
				na MCI	38.5	8.45	49	54	10	52	39	

p-tau, phosphorylated tau; aMCI, amnestic mild cognitive impairment; naMCI, non amnestic mild cognitive impairment; AD, alzheimer's disease; other, other type of dementia; SD, standard deviation; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

(n = 60), those not for Alzheimer's disease (n = 62), those revealed improper outcomes (n = 30), those without group comparison (n = 18) and those written before 2004 (n = 12) were also excluded. Finally, 8 studies were selected for this study (Fig. 1) [10-18]. The basic information of these studies were described in Table 4.

Systemic review of literature

Amnestic mild cognitive impairment (aMCI) versus non amnestic mild cognitive impairment (naMCI)

According to systemic review about clinical value of p-tau$_{181}$ was 48.6 ± 23.65-100 ± 25 pg/mL for aMCI and 38.5 ± 8.4-70.0 ± 27.0 pg/mL for naMCI [15, 17]. The prediction of conversion from aMCI to AD was reported by 1 study as 40.0%. The diagnostic accuracy was 0.51-0.87 for the sensitivity and 0.33-0.79 for the specificity (Table 4).

Alzheimer's disease versus healthy subjects

Clinical values of p-tau$_{181}$ was described in 6 studies as 63.5 ± 40.3-98.0 ± 25 pg/mL for AD and 24.8 ± 5.9-46.5 ± 9 pg/mL for healthy subjects. The diagnostic accuracy was 0.74-1.00 for the sensitivity and 0.65-0.91 for the specificity (Table 4).

Alzheimer's disease versus other dementia

Clinical values of p-tau$_{181}$ was described in 8 studies as 63.5 ± 40.3-98.0 ± 25 pg/mL for AD and 18.8 ± 6.7-51 ± 45.0 pg/mL for healthy subjects. The diagnostic accuracy was 0.77-0.86 for the sensitivity and 0.42-0.96 for the specificity (Table 4).

Comparing 95% confidence interval of each clinical group using mean value and standard deviation, the values of p-tau$_{181}$ in healthy subjects was overlapped with those of other clinical groups as well as diseased group themselves (Fig. 2)

Meta-analysis

The funnel plot to confirm the publication bias is shown in Fig. 3.

aMCI versus naMCI

The p-tau$_{181}$ concentration of CSF is increased in naMCI compared to aMCI but heterogeneity was high (I^2 = 63%) (Table 5). Mean sensitivity values was 0.556 (with 95% CI 0.464-0.644, χ^2 = 6.68(p = 0.035), I^2 = 70.1%) and mean specificity values was 0.723 (with CI 0.598-0.827, χ^2 = 27.43(p < 0.001), I^2 = 92.7%). The Summary Receiver Operating Characteristic Area Under the Curve (SROC AUC) was 0.7176 ± 0.0623 (Fig. 4).

Alzheimer's disease versus healthy subjects

The p-tau$_{181}$ concentration of CSF is increased in AD compared to healthy subjects but heterogeneity was very high (Mean difference: -35.19 (with 95% CI -39.76~-32.62, p < 0.001, I^2 = 87%, effect Z = 25.82) (Table 5). Mean sensitivity values was 0.844 (with 95% CI 0.810-0.874, χ^2 = 20.23(p = 0.003), I^2 = 70.3%) and mean specificity values was 0.769 (with CI 0.726-0.807, χ^2 = 26.11(p < 0.001), I^2 = 77.0%). The SROC AUC was 0.8971 ± 0.0234 (Fig. 4).

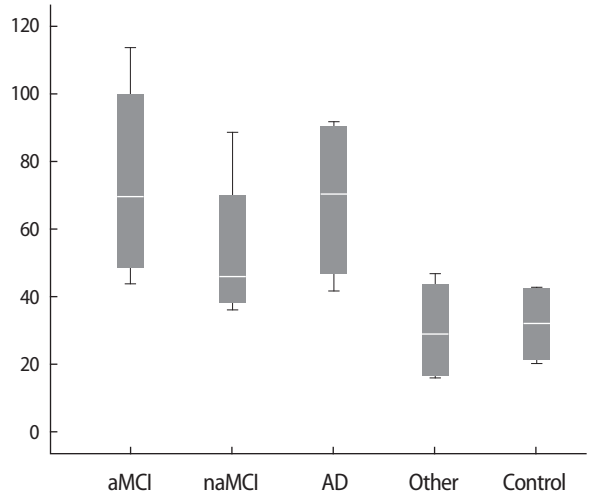


Fig. 2. 95% confidence interval of each clinical group using mean value and standard deviation.

Alzheimer's disease versus other dementia

The p-tau$_{181}$ concentration of CSF is decreased by 42.24 pg/mL in the other dementia compared to AD but heterogeneity was high (I^2 = 61%) (Table 5). Mean sensitivity values was 0.843 (with 95% CI 0.818-0.876, χ^2 = 13.82(p = 0.055), I^2 = 49.3%) and mean specificity values was 0.799 (with CI 0.768-0.828, χ^2 = 38.72(p < 0.001), I^2 = 81.9%). SROC AUC was 0.9082 ± 0.0236 (Fig. 4).

DISCUSSION

The purpose of this study is to evaluate the value of the p-tau$_{181}$ in CSF for the differential diagnosis of AD from other type of dementia as well as from normal control. It is somewhat controversial concerning the usability or cut-off value of the CSF p-tau because there was some discrepancy according to previous reports and it might be derived from the variability of sample acquisition, processing or repository method [19]. There are already reported well-organized meta-analysis for CSF p-tau and meta-review for all CSF biomarker of AD [9, 20] but they did not focus on the CSF p-tau$_{181}$ which is clinically available in Korea. So, we tried to focus on the evaluation of it. Eight analyses were previously reported regarding the value of CSF p-tau$_{181}$ concentration as a biomarker of

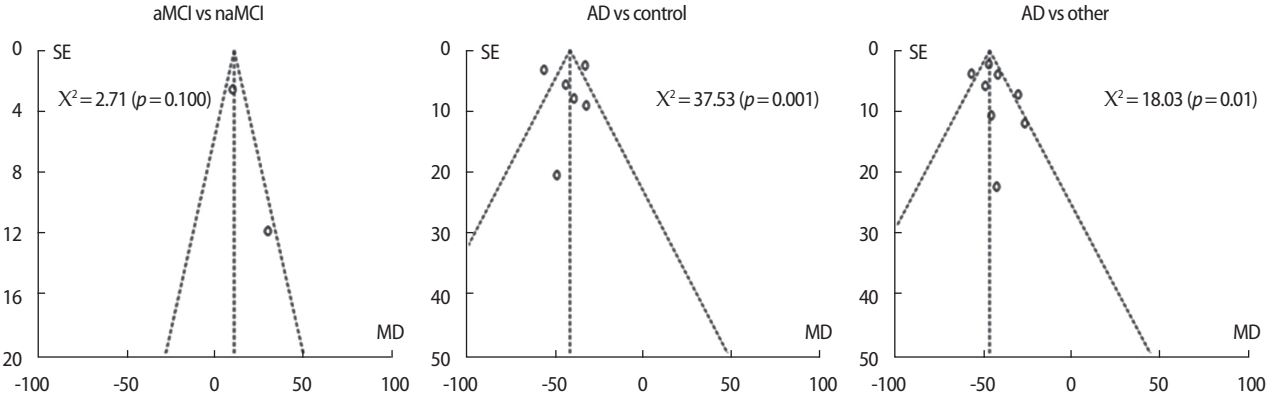


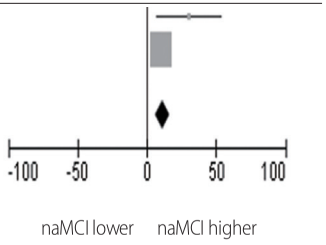
Fig. 3. Funnel plot of selected studies.

Table 5. Diagnostic meaning of Phosphorylated tau 181

aMCI vs naMCI

Study	naMCI			aMCI			Weight	Mean difference 95% CI
	Mean	SD	Total	Mean	SD	Total		
Herukka+ (2008)	100	25	13	70	27	8	4.6%	30.00 [6.88, 53.12]
Lewczuk (2008)	48.6	23.65	106	38.5	8.45	49	95.4%	10.10 [5.01, 15.19]
Total (95% CI)			119			57	100.0%	11.02 [6.05, 15.99]

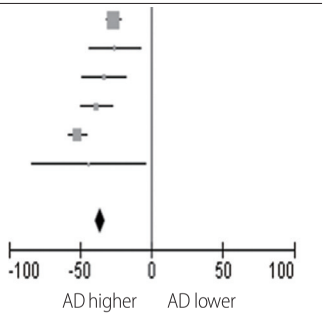
Heterogeneity: Chi square = 2.71, df = 1 ($p = 0.100$); $I^2 = 63\%$
Test for overall effect: Z = 4.35 ($p < 0.001$)



AD vs control

Study	Control			AD			Weight	Mean difference 95% CI
	Mean	SD	Total	Mean	SD	Total		
Kapaki (2007)	45.1	7.9	72	19.8	19.8	67	49.4%	-26.9 [-31.98,-21.82]
Le Bastard (2013)	40	57	95	50	50	51	4.0%	-26.00 [-43.88,-8.12]
Park (2013)	46.5	9	12	31	31	17	5.2%	-33.50 [-49.09,-17.91]
Ravaglia (2009)	24.8	5.9	36	40.3	40.3	51	10.1%	-38.70 [-49.93,-27.47]
Reijin (2007)	46	10	55	25	25	69	30.5%	-52.00 [-58.46,-45.54]
Schoonenboom (2004)	35	34.5	21	130.5	130.5	47	0.8%	-44.00 [-84.12,-3.88]
Total (95% CI)			291			302	100.0%	-36.19 [-39.76,-32.62]

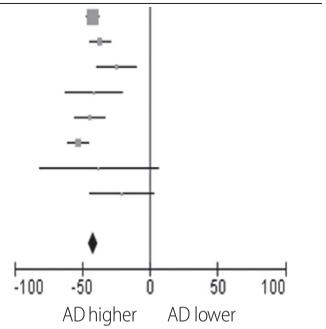
Heterogeneity: Chi square = 31.53, df = 5 ($p < 0.001$); $I^2 = 87\%$
Test for overall effect: Z = 19.87 ($p < 0.001$)



AD vs other

Study	Other			AD			Weight	Mean difference 95% CI
	Mean	SD	Total	Mean	SD	Total		
Dumurgier (2013)	49.6	28	365	92.1	41.9	515	48.2%	-42.50 [-47.12,-37.88]
Kapaki (2007)	34.8	13.35	18	72	19.8	67	17.0%	-37.20 [-44.98,-29.42]
Le Bastard (2013)	41	19.5	95	66	50	51	5.0%	-25.00 [-39.27,-10.73]
Park (2013)	38.6	22.6	9	80	31	17	2.4%	-41.40 [-62.26,-20.54]
Ravaglia (2008)	18.8	6.7	19	63.5	40.3	51	7.8%	-44.70 [-56.16,-33.24]
Reijin (2007)	45	13	26	98	25	69	17.2%	-53.00 [-60.73,-45.27]
Schoonenboom (2004)	41	61.5	28	79	130.5	47	0.5%	-38.00 [-81.71,-5.71]
Stefani (2005)	51	45	20	72	53	66	1.9%	-21.00 [-44.50,2.50]
Total (95% CI)			580			883	100.0%	-42.24 [-45.45,-39.04]

Heterogeneity: Chi square = 18.03, df = 7 ($p = 0.010$); $I^2 = 61\%$
Test for overall effect: Z = 25.82 ($p < 0.001$)



aMCI, amnestic mild cognitive impairment; naMCI, non amnestic mild cognitive impairment; AD, alzheimer's disease; other, other type of dementia; SD, standard deviation; CI, confidence interval.

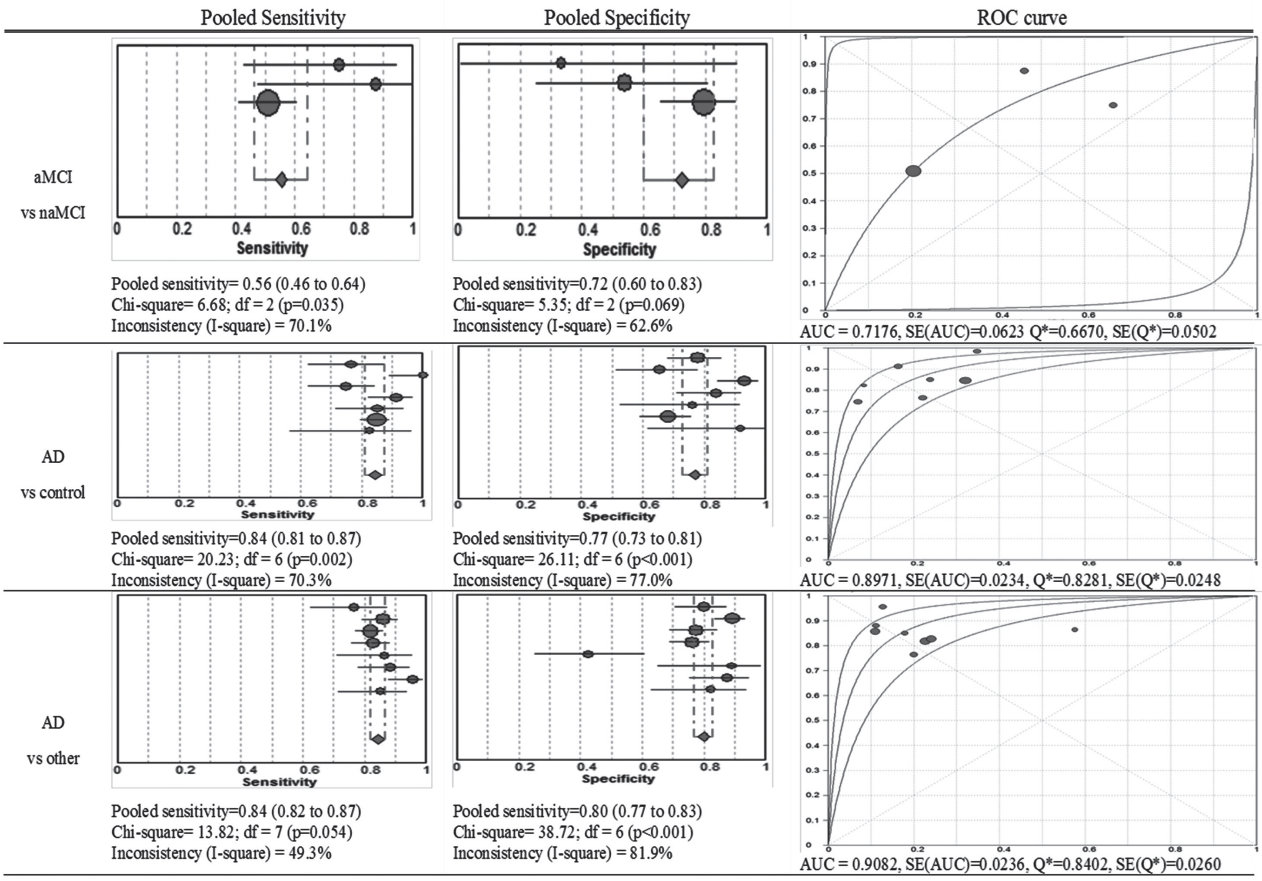


Fig. 4. Forest plot of sensitivities and specificities and Receiver operating characteristics (ROC) curve.

AD, MCI or other dementia. CSF p-tau$_{181}$ showed good differentiation between AD versus healthy subject. According to our meta-analysis, discrimination was revealed by sensitivity and specificity value of 84.4% and 76.9%, respectively and there was some difference of the value of previously reported one by 77.6% and 87.9% [20] although it was about p-tau regardless of its epitope (p181, p199 or p231). The CSF p-tau$_{181}$ also showed good differentiation between AD and other dementia represented by sensitivity and specificity value of 84.3% and 79.9%. The development of more specific biomarkers for these disorders is needed because some study suggested that biomarker of AD should obtain sensitivity and specificity of 75-80% or greater [21].

According to the systemic review, CSF p-tau$_{181}$ concentrations in other dementia such as dementia with Lewy body, frontotemporal lobar degeneration and vascular dementia was intermediate between the value of controls and AD patients. However, the values of p-tau$_{181}$ in healthy subjects were overlapped with those of other clinical groups. This overlap between control group and AD patients results insufficient diagnostic accuracy, therefore it is necessary to develop more specific biomarkers or methodology of processing CSF biomarker for these disorders.

This study has some limitations. The number of studies included in this systemic review and meta-analysis is somewhat small as eight studies. And the heterogeneity and bias represented by I^2 and funnel plot and was high and it might be derived from the factors such as variability of CSF sample processing technology followed by different cut-off value according to different clinical centers or small study number described above. On top of it, it is possible that there might be some errors of recruitment stage because the patients' characteristics are not always provided in the literature. The absence of a technical standardization also might be the cause of vari-

ability in cut-off values for CSF biomarker [9]. Recently new methodologies have been reported to reduce the inter- and intra-assay variability compared to conventional method such as ELISA [22]. Standardization processes are essential to get validity in the result of CSF biomarker, but it is not achieved at present so some suggestions such as proposed normalized index or systemic normalization method have been reported [23, 24]. Moreover, comparison between AD and MCI was not considered in the current meta-analysis although it might be useful but still unclear.

This meta-analysis with systemic review described the p-tau$_{181}$ among core CSF biomarkers of AD to discriminate AD from normal healthy controls and AD from other dementia groups. Although, a large number of studies reported to validate CSF biomarkers, it is not suitable for its general application in clinical setting as diagnostic criteria [25]. The clinical diagnosis is still essential and biomarkers are complementary [2]. This study confirmed the CSF p-tau$_{181}$ suitable for the discrimination of AD and normal control but showed weakness to differentiation between AD and other dementia. Because general use of CSF biomarker in clinical setting would be very important for early diagnosis as well as monitoring disease progression, the further evaluation of validity of currently accepted tool such as CSF p-tau might be useful.

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