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Systematic Review and Meta-Analysis of Diagnostic Alzheimer's Disease with Blood Biomarkers

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Abstract

Background: One of the world's leading causes of death is Alzheimer's disease (AD). Diagnostic of the disease and determining the risk before it reaches a severe stage are essential to reduce the rate of a patient's development into the dementia phase, as well as locating practical, economical, and effective diagnostic tools, including blood tests, are easier and still reasonably priced, compared to neuroimaging or cerebrospinal fluid (CSF) examinations.

Method: The studies were systematically searched for and determined by pooled sensitivity and specificity which studies were_about diagnosing AD using the single molecular array (SIMOA) method by detecting phosphorylated tau (p-tau) in the blood. In addition, Egger's test results for heterogeneity and publication bias were evaluated.

Result: After systematically review the studies from 2016 to 2023, seven studies have been included for the meta-analysis. The results show low level of heterogeneity (I^2 = 28.99%) and no publication bias Egger's test in sensitivity and specificity (*p*-value = 0.244 and 0.084, respectively) in patients.

Conclusion: The ability to identify p-tau in blood with SIMOA has been useful in the diagnosis of Alzheimer's disease. Currently, this procedure is utilized in conjunction with other diagnostic approaches for diagnosis.

Keywords: Alzheimer's disease, Blood biomarker, Phosphorylated tau, Diagnosis, Meta-Analysis

What was Known

- Phosphorylated tau is one of the protein biomarkers used for diagnosing Alzheimer's disease, commonly found in cerebrospinal fluid and blood.
- Sensitivity and specificity measured the effectiveness of the diagnostic tool.

What's New and Next

- Recognizing the efficacy of diagnostic instruments offers a multiplicity of diagnostic alternatives and amplifies the productivity of current diagnostic techniques.
- The scope of the research can be expanded to encompass additional categories of biomarkers.

Introduction

The World Health Organization (WHO) has identified AD, a kind of dementia, as one of the top 10 causes of death worldwide in its 2020 report[1]. It has been discovered that as the population ages, there is an increasing annual incidence of AD, particularly in the form of Alzheimer's dementia, the disease's terminal stage. Anders Gustavsson et al.[2] forecasts in 2022 indicate that the global prevalence rate of dementia is predicted to rise from 27 million cases in 2006 to 32 million cases globally. Consequently, AD, which is an incurable ailment that worsens with age, has been recognized in this research. Getting a diagnostic makes people aware of their personal risk, which may enable them to more effectively slow down the disease's progression.

A review study which conducted in 1965 found that a variety of techniques, including neuroimaging such as computed tomography (CT scan), positron emission tomography (PET), or spectroscopy, were used to diagnose Alzheimer's disease at that time. The diagnostic procedure also included behavioral evaluations and psychiatric testing. Zaven S. Khachaturian[3] did point out that post-mortem brain examinations would yield the most precise diagnosis. Despite its excellent accuracy, this approach does not offer a prophylactic measure. In an effort to improve diagnostic accuracy, attention has switched to investigating non-invasive techniques, such as the investigation of body fluids like CSF, urine, saliva, or blood. CSF was the first focus of body fluid diagnostic test because of its close proximity to the brain. However, compared to drawing blood, the process of extracting CSF from individuals is more involved. The development of more practical techniques like immunoassays has made it possible to diagnose the underlying causes of diseases, including Alzheimer's, much more easily. These developments in diagnostic technologies have made this possible[4]. Immunoassays are intended to identify proteins, such as

neurofilament light chain protein, total tau, phosphorylated tau, and amyloid biomarkers, that function as disease indicators.

The effectiveness of phosphorylated tau (p-tau) detection in blood has been noted as having great diagnostic potential, which is the reason of the research is interested in the protein's ability for detection. The area under the curve (AUC) values for p-tau in blood have been shown to be extraordinarily high, ranging from 99.40% to 100%, based on data collection. The AUC values for blood p-tau are greater than 75% when contrasted with detection techniques utilizing PET or CSF[5]. Joyce R. Chong et al.[6] have mentioned that p-tau has high sensitivity in distinguishing people with AD from Non-AD in their review. Additionally, another review of Thomas K. Karikari et al.[7] have indicated that blood p-tau concentrations are associated with other biomarkers like Amyloid-beta or neurodegeneration with the ability to detect AD, both in CSF and PET testing. In the single molecular array (SIMOA) part, one of the diagnostic methods using biomarkers found that it is more effective in detecting p-tau than Amyloid-beta and t-tau, with an AUC of 83% and high sensitivity and specificity values of 85% and 70%, respectively. Meanwhile, Amyloid-beta and t-tau have sensitivity values of less than 60%[8].

This research used the SIMOA approach to perform a systematic review and meta-analysis on the p-tau biomarker extracted from blood. The aim is to evaluate its efficacy in diagnosing diseases, offering a substitute for Alzheimer's diagnosis that permits patients to obtain more precise screening while preserving affordability and ease of use. It might also be used to confirm accuracy and estimate the probability that a patient would develop a condition in addition to being used in conjunction with other diagnostic techniques.

Materials and Methods

This research was registered in the Prospective Register of Systematic Reviews (PROSPERO) with registration number: CRD42024507686. The PRISMA flow diagram[9] which was material used to include and exclude papers from databases is followed in the reporting of this research.

1.Inclusion and exclusion criteria

The inclusion criteria included the following:

1.) The study participants were diagnosed with AD dementia.

2.) Cohort studies

3.) The study was only published in English between 2016 and 2023.

4.) The diagnostic tool for AD was the SIMOA technique using blood, employing phosphorylated-tau as biomarkers

5.) The value assessing the accuracy of diagnostic tools (sensitivity, specificity) was the study's outcome.

In the exclusion criteria, studies that did not have a defined case and control group, did not have sensitivity/specificity values or participant counts, were review papers, did not involve human subjects, or were not written in English were eliminated.

2. Search strategy and selection criteria

According to the inclusion criteria, four databases—PubMed, Scopus, EMBASE, and MEDLINE—were searched between 2016 and 2023. “Alzheimer OR AD AND Biomarker AND Diagnosis AND SIMOA OR single molecular array” was the search term entered into the databases.

3.Data analysis

Sensitivity and specificity are the effect measures used in the research to evaluate the SIMOA method's accuracy. Calculating the (1) sensitivity, (2) specificity, and (3) false positive rate that Jacob Yerushalmy[10] originally interpreted can be performed by

Sensitivity calculated by "True positive participants"/ "True positive participants compound with False negative participants"

Specificity calculated by "True negative participants" /"True negative participants compound with False positive participants"

False positive rate calculated by 1- specificity

In order to calculate overall sensitivity and specificity with confidence interval (CI), heterogeneity, and create forest plots and summary receiver operating characteristic (SROC) curves of all included studies in the biomarker result, STATA 17 software (licensed to the

biostatistics, public health faculty, Mahidol university) which was installed by the 'Metadta' command package[11] was used. I^2 and Tau-square (T^2) statistics were used to evaluate the heterogeneity of the studies. I^2 more than 50% showed that the random-effect model should be recommended because there is substantial heterogeneity in the meta-analysis. R program version 4.3.0 was used to verify the asymmetry test using Funnel plot and Egger's test. The 'MVPBT' package[12] was installed before verification. Typically, a Funnel plot is used for visual analysis, while Egger's test is used to recheck the assessment of publication bias. Research of Chuan Hong et al.[13] suggests that this approach is suitable for multi-variable meta-analysis, as in this research. The variables used in the calculation include logit-transformed sensitivity and false positive rate (FPR) as follows:

Logit (sensitivity) = ln (sensitivity) – ln (1-sensitivity)

Logit (FPR) = ln (FPR) – ln (1-FPR)

Three authors (NK, HC, and ST) then evaluated each of the resulting studies' titles separately to determine their applicability. One of the authors, HC, has conducted numerous meta-analysis research investigations in the past[14, 16]. The papers that were deemed potentially relevant were subjected to the inclusion and exclusion criteria in the abstract section so that their inclusion in the meta-analysis could be assessed. Seven studies were chosen for the meta-analysis based on the search results and inclusion criteria **(Table 1)**. Information that NK, HC, and ST took out of the included studies. R version 4.3.0 software was used to assess the risk of bias in seven studies that used the QUADAS-2 tool[17].

Results

1. Selection diagram (PRISMA flowchart)

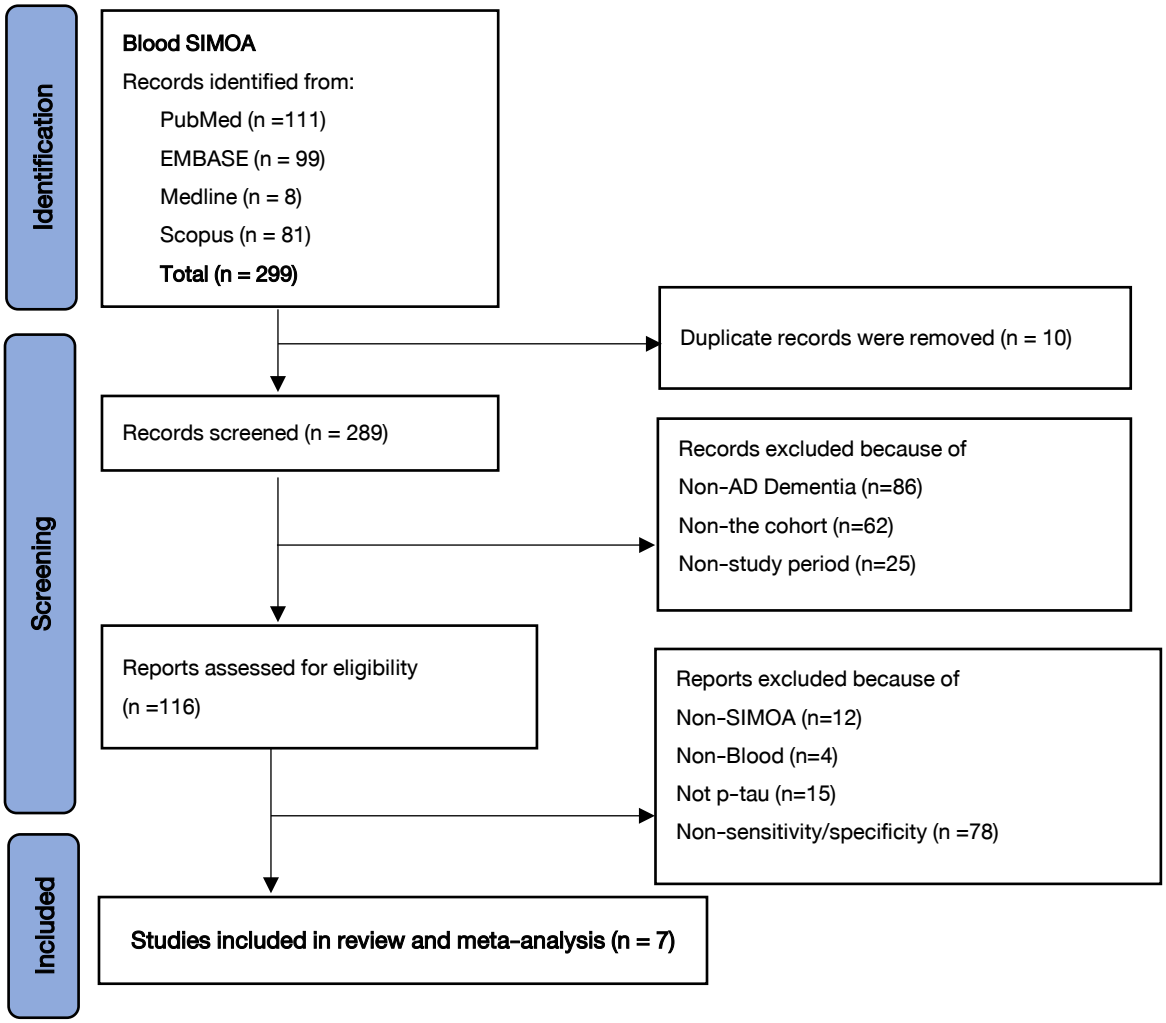

Figure 1. PRISMA flow diagram for systematic reviews and meta-analysis

2. Study characteristics

The seven studies were from the Netherlands (28.57%) and other countries (The United States, Japan, Singapore, Germany, Australia and Italy) included in the meta-analysis (Table 1). A total of 13 observations were identified as an AD diagnostic tool in blood SIMOA. 13 observations from 7 studies in p-tau.

Table 1.7 included studies of meta-analysis for AD patients.

Study	Patient population (n)	Control population (n)	Reference standard criteria	Sensitivity	Specificity
Simone Baiardi et al. 2022[18]	97	168	N/A	86.6	80.0
Denis S. Smirnov et al. 2022[19]	124	29	NIA-AA	73	86.7
Elisabeth H. Thijssen et al. 2022[20]	36	38	clinical criteria	74	97
	38	38		66	76
	38	38		76	76
Patrick Oeckl et al. 2022[21]	74	31	N/A	77	71
		81		82	75
		41		82	65
		55		77	80
Pratishtha Chatterjee et al. 2022[22]	46	81	NINCDS-ADRDA	89.1	87.7
		26		91.3	92.3
Sherif Bayoumy et al. 2021[23]	40	40	NIA-AA	89	90
Harutsugu Tatebe et al. 2017[24]	20	15	NINCDS–ADRDA	60	85.7

3. Risk of bias

The risk of bias was assessed using QUADAS-2 across four categories: (1) Patient selection, (2) Index test, (3) Reference standard and (4) Flow & timing. Overall of the risk of bias was 6 low-risk and 1 some concerns.

4. Forest plot and SROC Curve

In part of diagnosed AD by detecting p-tau **(Figure 2-4)** displayed low level of heterogeneity (I^2 = 28.99%, T^2 = 0.02%) in generalized form. The *p*-value of Chi-squared statistics of all groups which was all control groups was significant in 95% confidence interval that means this model was suitable to random effect model. The overall of sensitivity and specificity were 81% (CI: 74%-87%) and 83% (CI: 77%-87%), respectively. In addition, control group is only other diseases group, it displayed low of heterogeneity (I^2 = 24.28%, T^2 = 0.01%) and sensitivity and specificity were 81% (CI: 74%-86%) and 82% (CI: 76%-86%), respectively. However, due to the fact that are only two studies available, the healthy control group is unable to estimate the heterogeneity value.

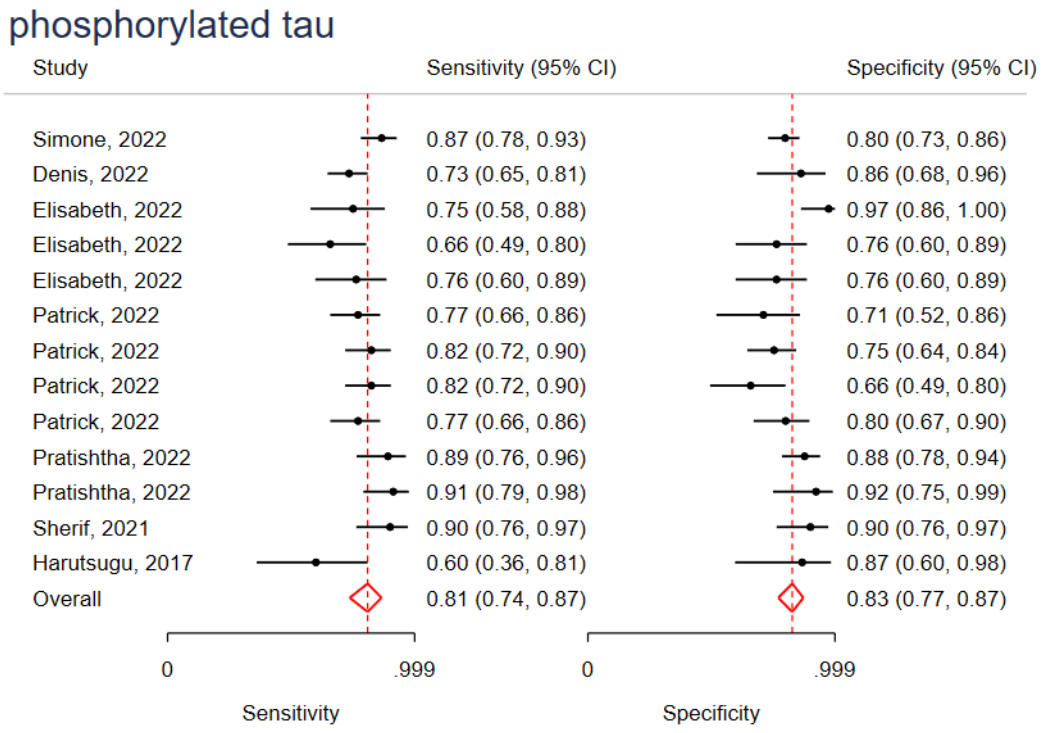

Figure 2. Forest plot for AD patients of p-tau

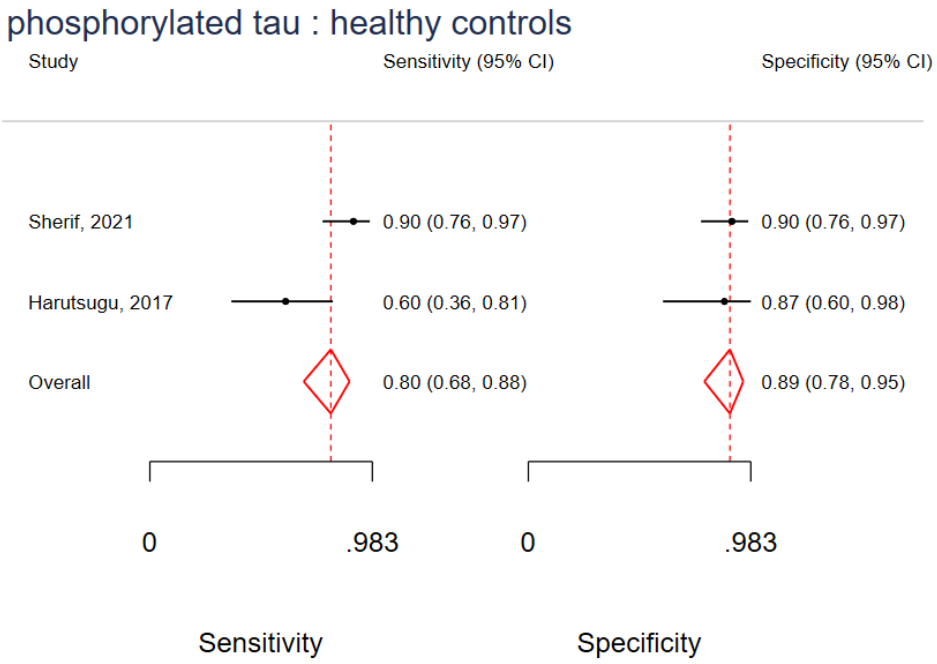

Figure 3. Forest plot for AD patients of p-tau which healthy controls are control groups

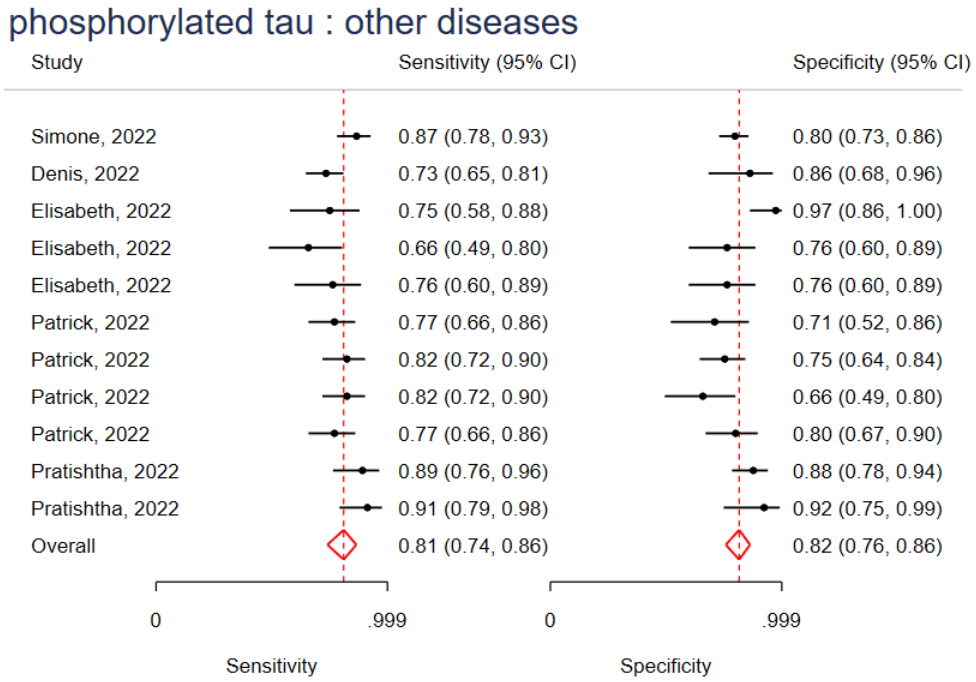

Figure 4. Forest plot for AD patients of p-tau which healthy controls are other diseases.

The summary receiver operating characteristic (SROC) Curve showed the association of sensitivity and specificity of blood SIMOA method. area under the curve (AUC) value for AD patients was 0.865 in p-tau, respectively. In part of other diseases is control group, AUC for AD patients was 0.858 in p-tau. AUC value for AD patients which healthy control is control group was 0.902 in p-tau. The results of blood SIMOA showed that the AUC values for p-tau seem to be better in the control group, which comprises healthy individuals.

5. Publication bias

The result of univariate Egger's test **(Figure 5-6)** showed that there was no publication bias for sensitivity of AD patients in p-tau (*p*-value = 0.244) in 95% confidence interval. The *p*-value of false positive rate as a result of univariate Egger's test showed that there was no publication bias in p-tau (*p*-value = 0.084) in 95% confidence interval. Aβ and t-tau had 1 study in each group so they did not enable to test publication bias.

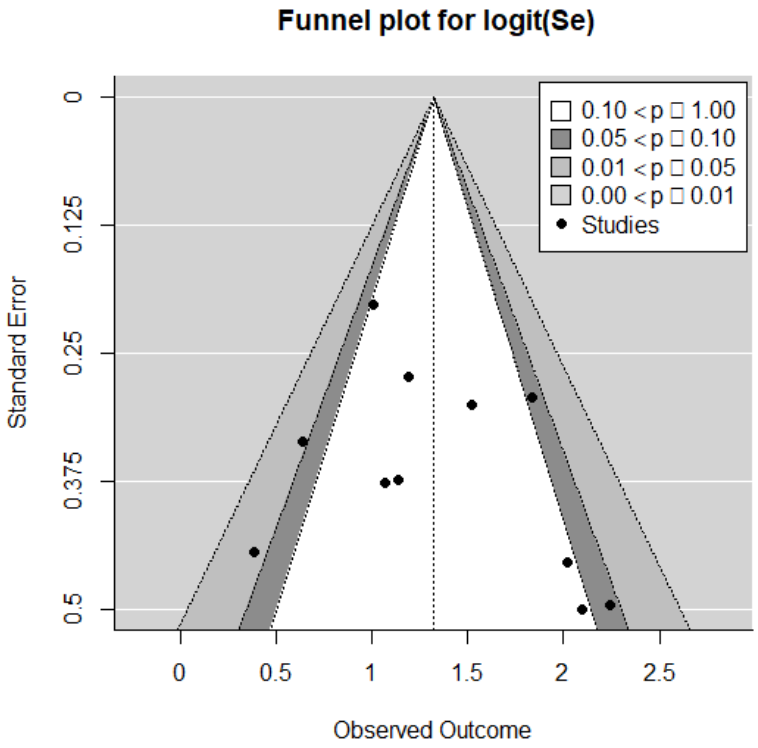

Figure 5. Logit-transformed sensitivity funnel plot of p-tau.

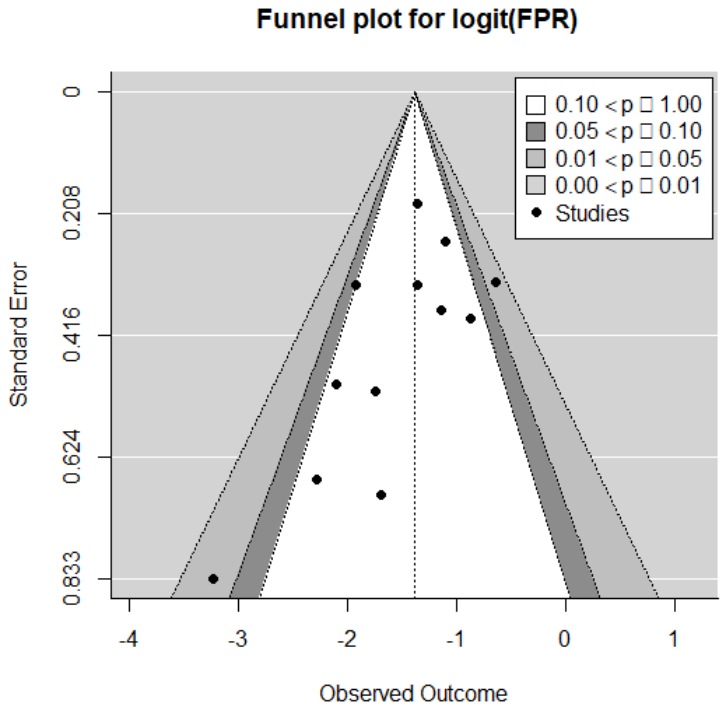

Figure 6. Logit-transformed false positive rate funnel plot of p-tau.

Discussion

This research conducted meta-analysis in the blood SIMOA as same as CSF ELISA across three biomarker groups: Aβ, *p*-tau, and t-tau. The values for heterogeneity, chi-squared test, and forest plot for the Aβ and t-tau groups could not be established due to the insufficient number of studies. The limited studies on Amyloid-beta and total tau were attributed to conflicting results in various studies, Jordi Sarto et al.[25] mentioned that in each diagnostic study involving blood Amyloid-beta and total tau, there have been contradictory outcomes. Additionally, Geethu Krishna et al.[8] found that sensitivity of blood Amyloid-beta and total tau values below 60%, which could be a reason why the researchers are not incorporating both biomarkers as extensively as p-tau in diagnostics.

P-tau has shown promise in the detection of AD, with pooled sensitivity and specificity values above 80% (81% and 83%, respectively) and an AUC of SROC value close to 1 (AUC = 0.87). The pooled sensitivity and specificity of the current study compared with meta-analysis in blood SIMOA with P-tau181 of Xulong Ding et al.[26] showed the results that 0.89 and 0.86, respectively. The results of these research show that the sensitivity and specificity are both higher than 80%. However, in the research conducted by Xulong Ding et al., the values were higher than our research, possibly because their research focused exclusively on the distinctive diagnostic value of P-tau 181 in AD. In contrast, this study included all forms of P-tau, whether *P*-tau 181 or *P*-tau 231.

The found heterogeneity was 95% when comparing the heterogeneity values of Leian Chen et al.'s meta-analysis[27] on the diagnosis of AD by using blood with the detection of P-tau, which included not only SIMOA but also ELISA and IMR. On the other hand, the heterogeneity value for blood SIMOA in this investigation was about 29% and Egger's test of sensitivity and specificity are no publication bias (p-value > 0.05) compared with meta-analysis of Ivan Koychev et al.[28] had different Egger's test result from our results that there had publication bias (p-value < 0.05), however they used another effect size like biomarker concentrations which could have led to different results.

When dividing the control group into "other diseases" and "healthy people," it was found that the results for the control group of healthy people had only 2 studies, making it impossible to determine heterogeneity. The reasons for the popularity of research using P-tau to diagnose AD from non-AD patients, Ling Wu et al.[29] explained that P-tau is highly accurate, contributing

significantly to its popularity. Therefore, using P-tau for the diagnosis of AD has become highly favored. This is why research on *P*-tau for diagnosing AD is often paired with a control group that includes individuals with other diseases, and this pairing tends to have a larger number than paired with healthy controls group. The heterogeneity value for the other diseases control group was at a low level, decreasing from the all control group to 24.28%. The overall sensitivity and specificity values did not differ significantly compared with all control group, with values of 81% and 82%, respectively.

Our research employed blood SIMOA techniques to demonstrate the efficacy of a method that reduced bias from alternative approaches, demonstrated blood SIMOA diagnostic capabilities, and improved diagnostic accuracy prior to MRI or CT scan diagnosis. The study also highlighted the affordability and ease of use of using blood as a bodily fluid that is more than CSF or neuroimaging[30] as the primary criterion for diagnostic decision-making. There are some limitations on our study. The studies with a healthy control group that are included are not enough and most studies did not show the results in sensitivity and specificity form. Next step, comparing blood SIMOA with other bodily fluid tests to determine AD dementia might be helpful for future research.

Conclusion

Non-invasive, inexpensive, and highly effective blood-based methods of diagnosing AD, particularly with regard to biomarkers like p-tau, an interesting biomarker present in both CSF and blood, offer a promising substitute to slow the development of the AD dementia and give patients more access to diagnostic testing.

Ethical Approval Statement

This research has been approved according to the Standard Operating Procedures of Ethical Review Committee for Human Research, Faculty of Public Health, Mahidol University.

Author Contributions

The study was performed and analyzed under the supervision of HC. The manuscript is written by NK and revised by HC. All authors read and approved the manuscript prior to submission for the publication.

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Conflicts of Interest

The authors declare to have no conflicts of interest.

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