INPLASY

Accuracy and Influencing factors of Urinary AD7c-NTP for Diagnosing Alzheimer's Disease: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - Data extraction.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202530048

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 March 2025 and was last updated on 11 March 2025.

INTRODUCTION

Review question / Objective What is the diagnostic performance of urinary AD7c-NTP for Alzheimer's disease, and what is the optimal cut-off value? What are the factors that influence the level of urinary AD7c, and what are the optimal cut-off values for diagnosis when subgroups are divided based on these factors?Is it feasible to diagnose Alzheimer's disease through urinary AD7c-NTP?

Rationale Alzheimer's disease (AD) is a degenerative disorder of the central nervous system that primarily affects brain function, leading to progressive cognitive impairment and behavioral damage. The disease is characterized by a comprehensive range of dementia symptoms, including memory impairment, aphasia, apraxia, agnosia, visuospatial skill impairment, executive dysfunction, and personality and behavioral changes. AD can be classified into mild, moderate, and severe stages. Additionally, amnestic mild cognitive impairment (aMCI) related to Alzheimer's disease is widely regarded as a transitional phase of AD. As there is currently no cure for Alzheimer's disease, timely diagnosis of AD or diagnosis of aMCI with the aim of slowing disease progression becomes particularly important. Diagnostic methods can be broadly categorized into psychopathological assessments, imaging examinations, and biomarker tests. Given the invasive nature of traditional cerebrospinal fluid biomarker diagnosis, there is an urgent need for a new diagnostic marker that can serve as a diagnostic or auxiliary diagnostic tool. Through extensive literature review, several markers detected in blood, saliva, and urine have emerged. However, none of them have been formally adopted for clinical use. Among these, Alzheimer's disease-associated neuronal thread protein (AD7c-NTP) in urine is a potential diagnostic marker, but its diagnostic efficacy has not been fully proven, and factors influencing the variation in urinary AD7c-NTP levels are also controversial. This study aims to reasonably synthesize previous research, analyze the diagnostic efficacy of urinary AD7c-NTP for AD, and investigate the factors affecting

the variation in urinary AD7c-NTP levels, conducting subgroup analyses based on different influencing factors to aid in the diagnosis of AD.

Condition being studied Research on Biomarkers: The core biomarkers are β-amyloid protein (Aβ) and Tau protein. Currently, the diagnostic biomarkers in cerebrospinal fluid (CSF) offer the highest accuracy, and studies have shown that the diagnosis using these two substances in plasma also has high accuracy and is non-invasive. Other potential biomarkers, such as AD7c-NTP and exosomes, are strongly associated with Alzheimer's disease (AD). Imaging Techniques: Positron emission tomography (PET) can visually display the deposition of Aβ in the brain, aiding in the early diagnosis of AD. It also assesses the distribution and aggregation of Tau protein in the brain, which is significant for the diagnosis and monitoring of AD. Other imaging techniques, such as structural magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), can also provide supplementary information for the diagnosis of AD. Multimodal Diagnosis: Combining multimodal information from biomarkers, imaging techniques, and neuropsychological assessments can improve the accuracy of AD diagnosis. The use of artificial intelligence (AI) assists in enhancing diagnostic accuracy.

METHODS

Search strategy We searched a total of 15 databases in both Chinese and English.We searched a total of 15 databases.China National Knowledge Infrastructure;China Science and Technology Journal Database; Wanfang Data; Duxiu library;CBM;Chinese Clinical Trial Registry; PubMed;Web of science;PROquest;ovid;scopus;ClinicalTrials;The Cochrane Library;embase.Terms:Alzheimer Disease;Alzheimer Syndrome;Alzheimer-Type Dementia (ATD);Alzheimer Type Dementia (ATD);Dementia, Alzheimer-Type (ATD);Alzheimer's Diseases;Alzheimer Diseases;Alzheimers Diseases;Alzheimer Dementia;Alzheimer Dementias;Dementia, Alzheimer;Alzheimer's Disease;Dementia, Senile;Senile Dementia;Dementia, Alzheimer Type;Alzheimer Type Dementia;Senile Dementia, Alzheimer Type;Alzheimer Type Senile Dementia;Primary Senile Degenerative Dementia;Alzheimer Sclerosis;Sclerosis, Alzheimer;Dementia, Primary Senile Degenerative;Dementia, Presenile;Presenile Dementia;Acute Confusional Senile Dementia;Senile Dementia, Acute Confusional;Alzheimer Disease, Early Onset;Early Onset Alzheimer Disease;Presenile Alzheimer Dementia;Alzheimer Disease, Late Onset;Late Onset Alzheimer Disease;Alzheimer's Disease, Focal Onset;Focal Onset Alzheimer's Disease;Familial Alzheimer Disease (FAD);Alzheimer Disease, Familial (FAD);Familial Alzheimer Diseases (FAD);Mild cognitive impairment;mci ad;Subjective cognitive function declines;Alzheimer' sdisease;slight cognition disfunction;Dementia;cognitive impairment;cognitive dysfunction;Cognitive Dysfunctions;Dysfunction, Cognitive;Dysfunctions, Cognitive;Cognitive Disorder;Cognitive Disorders;Disorder, Cognitive;Disorders, Cognitive;Cognitive Impairments;Cognitive Impairment;Impairment, Cognitive;Impairments, Cognitive;Mild Cognitive Impairment;Cognitive Impairment, Mild;Cognitive Impairments, Mild;Impairment, Mild Cognitive;Impairments, Mild Cognitive;Mild Cognitive Impairments;Cognitive Decline;Cognitive Declines;Decline, Cognitive;Declines, Cognitive;Mental Deterioration;Deterioration, Mental;Deteriorations, Mental;Mental Deteriorations;AD7c-NTP protein;Alzheimer-associated neuronal thread protein;neuronal thread protein;AD7c-NTP;Sensitivity and Specificity;Specificity and Sensitivity;Sensitivity;Specificity.

Fifteen search queries have also been made, such as the PubMed search query:(Alzheimer Disease[MeSH Terms] OR Alzheimer Syndrome[Title/Abstract] OR Alzheimer-Type Dementia (ATD)[Title/Abstract] OR Alzheimer Type Dementia (ATD)[Title/Abstract] OR Dementia, Alzheimer-Type (ATD)[Title/Abstract] OR Alzheimer's Diseases[Title/Abstract] OR Alzheimer Diseases[Title/Abstract] OR Alzheimers Diseases[Title/Abstract] OR Alzheimer Dementia[Title/Abstract] OR Alzheimer Dementias[Title/Abstract] OR Dementia, Alzheimer[Title/Abstract] OR Alzheimer's Disease[Title/Abstract] OR Dementia, Senile[Title/Abstract] OR Senile Dementia[Title/Abstract] OR Dementia, Alzheimer Type[Title/Abstract] OR Alzheimer Type Dementia[Title/Abstract] OR Senile Dementia, Alzheimer Type[Title/Abstract] OR Alzheimer Type Senile Dementia[Title/Abstract] OR Primary Senile Degenerative Dementia[Title/Abstract] OR Alzheimer Sclerosis[Title/Abstract] OR Sclerosis, Alzheimer[Title/Abstract] OR Dementia, Primary Senile Degenerative[Title/Abstract] OR Dementia, Presenile[Title/Abstract] OR Presenile Dementia[Title/Abstract] OR Acute Confusional Senile Dementia[Title/Abstract] OR Senile Dementia, Acute Confusional[Title/Abstract] OR Alzheimer Disease, Early Onset[Title/Abstract] OR Early Onset Alzheimer Disease[Title/Abstract] OR Presenile Alzheimer Dementia[Title/Abstract]

OR Alzheimer Disease, Late Onset[Title/Abstract] OR Late Onset Alzheimer Disease[Title/Abstract] OR Alzheimer's Disease, Focal Onset[Title/Abstract] OR Focal Onset Alzheimer's Disease[Title/Abstract] OR Familial Alzheimer Disease (FAD)[Title/Abstract] OR Alzheimer Disease, Familial (FAD)[Title/Abstract] OR Familial Alzheimer Diseases (FAD)[Title/Abstract] OR Mild cognitive impairment[Title/Abstract] OR mci ad[Title/Abstract] OR Subjective cognitive function declines[Title/Abstract] OR Alzheimer' sdisease[Title/Abstract] OR slight cognition disfunction[Title/Abstract] OR Dementia[Title/Abstract] OR cognitive impairment[Title/Abstract] OR cognitive dysfunction[Title/Abstract] OR Cognitive Dysfunctions[Title/Abstract] OR Dysfunction, Cognitive[Title/Abstract] OR Dysfunctions, Cognitive[Title/Abstract] OR Cognitive Disorder[Title/Abstract] OR Cognitive Disorders[Title/Abstract] OR Disorder, Cognitive[Title/Abstract] OR Disorders, Cognitive[Title/Abstract] OR Cognitive Impairments[Title/Abstract] OR Cognitive Impairment[Title/Abstract] OR Impairment, Cognitive[Title/Abstract] OR Impairments, Cognitive[Title/Abstract] OR Mild Cognitive Impairment[Title/Abstract] OR Cognitive Impairment, Mild[Title/Abstract] OR Cognitive Impairments, Mild[Title/Abstract] OR Impairment, Mild Cognitive[Title/Abstract] OR Impairments, Mild Cognitive[Title/Abstract] OR Mild Cognitive Impairments[Title/Abstract] OR Cognitive Decline[Title/Abstract] OR Cognitive Declines[Title/Abstract] OR Decline, Cognitive[Title/Abstract] OR Declines, Cognitive[Title/Abstract] OR Mental Deterioration[Title/Abstract] OR Deterioration, Mental[Title/Abstract] OR Deteriorations, Mental[Title/Abstract] OR Mental Deteriorations[Title/Abstract]) AND (Sensitivity and Specificity[MeSH Terms] OR Specificity and Sensitivity[Title/Abstract] OR Sensitivity[Title/Abstract] OR Specificity[Title/Abstract]) AND ("AD7c-NTP protein, human" [Supplementary Concept]) OR (Alzheimer-associated neuronal thread protein, human[Title/Abstract] OR neuronal thread protein, human[Title/Abstract] OR AD7c-NTP[Title/Abstract] OR AD7C-NTP[Title/Abstract])

The Chinese search terms are as follows:阿尔兹海默病;阿尔采默病;阿尔采默氏病;阿尔采默型痴呆;阿尔采默氏痴呆;老年性痴呆症;阿耳茨海默病;阿耳兹海默氏病;阿耳兹海默型痴呆;阿耳兹海默性痴呆;早老性痴呆;早老性痴呆症;阿尔茨海默氏病;阿尔茨海默氏痴呆;老年性痴呆;老年痴呆;阿尔茨海默症;老年性精神病;阿兹海默病;阿兹海默症;老年痴呆症;老年前期痴呆;阿兹海默氏症;阿兹海默氏病;阿尔茨海默氏症;阿尔兹海默综合症;AD 早期病症;AD 源性轻度认知功能障碍;轻度认知功能障碍;轻度认知功能损害;轻度认知障碍;轻度认知功能损伤;轻度认知损害;轻度认知损伤;轻微认知功能损害;主观认知功能下降;主观认知功能障碍;主观认知下降;主观认知功能衰退;阿尔兹海默症;阿尔茨海默病;阿尔兹海默病;阿尔兹海默;阿尔茨海默;痴呆;迟发性阿尔茨海默病;家族性阿尔茨海默病;阿尔茨海默型痴呆;阿尔茨海默型老年性痴呆;早发性阿尔茨海默病;早老阿尔茨海默痴呆;轻度神经认知障碍;认知减退;精神衰退;认知损害;阿尔茨海默病痴呆;阿尔茨海默型老年痴呆;阿尔茨海默综合症;晚发性阿尔茨海默病;遗忘型轻度认知功能障碍;早老性阿尔茨海默病痴呆;AD7c-NTP;尿AD7c-NTP;诊断;前期诊断

such as the China National Knowledge Infrastructure search query：(SU='阿尔兹海默病' OR SU='阿尔采默病' OR SU='阿尔采默氏病' OR SU='阿尔采默型痴呆' OR SU='阿尔采默氏痴呆' OR SU='老年性痴呆症' OR SU='阿耳茨海默病' OR SU='阿耳兹海默氏病' OR SU='阿耳兹海默型痴呆' OR SU='阿耳兹海默性痴呆' OR SU='早老性痴呆' OR SU='早老性痴呆症' OR SU='阿尔茨海默氏病' OR SU='阿尔茨海默氏痴呆' OR SU='老年性痴呆' OR SU='老年痴呆' OR SU='阿尔茨海默症' OR SU='老年性精神病' OR SU='阿兹海默病' OR SU='阿兹海默症' OR SU='老年痴呆症' OR SU='老年前期痴呆' OR SU='阿兹海默氏症' OR SU='阿兹海默氏病' OR SU='阿尔茨海默氏症' OR SU='阿尔兹海默综合症' OR SU='AD 早期病症' OR SU='AD 源性轻度认知功能障碍' OR SU='轻度认知功能障碍' OR SU='轻度认知功能损害' OR SU='轻度认知障碍' OR SU='轻度认知功能损伤' OR SU='轻度认知损害' OR SU='轻度认知损伤' OR SU='轻微认知功能损害' OR SU='主观认知功能下降' OR SU='主观认知功能障碍' OR SU='主观认知下降' OR SU='主观认知功能衰退' OR SU='阿尔兹海默症' OR SU='阿尔茨海默病' OR SU='阿尔兹海默病' OR SU='阿尔兹海默' OR SU='阿尔茨海默' OR SU='痴呆' OR SU='迟发性阿尔茨海默病' OR SU='家族性阿尔茨海默病' OR SU='阿尔茨海默型痴呆' OR SU='阿尔茨海默型老年性痴呆' OR SU='早发性阿尔茨海默病' OR SU='早老阿尔茨海默痴呆' OR SU='轻度神经认知障碍' OR SU='认知减退' OR SU='精神衰退' OR SU='认知损害' OR SU='阿尔茨海默病痴呆' OR SU='阿尔茨海默型老年痴呆' OR SU='阿尔茨海默综合症' OR SU='晚发性阿尔茨海默病' OR SU='遗忘型轻度认知功能障碍' OR SU='早老性阿尔茨海默病痴呆') AND (SU='AD7c-NTP' OR SU='尿AD7c-NTP') AND (TKA='诊断' OR TKA='早期诊断').

Participant or population The patient group:Mild Cognitive Impairment, MCI;AD control group: nonamnestic MCI (naMCI),Normal population,Non-AD patients,non-MCI patients.

Intervention No.

Comparator No.

Study designs to be included Diagnostic accuracy studies.

Eligibility criteria If the literature meets the following conditions, it will be excluded:clear error in methodology;The reference standard for diagnosis is not specified;Urine Specimen Collection and Determination of Urinary AD7c-NTP Levels are not specified;The test duration, inclusion criteria for each group, and the number of participants are not specified;The number of participants in the trial is insufficient;There are issues with the inclusion and exclusion of participants in the trial, such as unreasonable exclusions;Exclusion of duplicate reports;The data is incomplete and the author cannot be contacted.

Information sources China National Knowledge Infrastructure;China Science and Technology Journal Database; Wanfang Data; Duxiu library; CBM; Chinese Clinical Trial Registry; PubMed; Web of science; PROquest; ovid; scopus; ClinicalTrials; The Cochrane Library; embase.

Main outcome(s) On November 27, 2024, the creation of fifteen database search queries and the retrieval of literature were completed, with a total of 404 articles retrieved and 220 articles remaining after deduplication. By March 2025, a final manual screening process yielded 60 articles containing complete data, which were then divided into two groups: AD group and aMCI group. The work is still ongoing.Two investigators independently extract the informations. When the same population was reported in several publications, we retain only the most informative article or the complete study to avoid duplication of information. Any disagreements should be resolved by discussion between the review authors. We will assesse study quality using the modified quality assessment for studies of diagnostic accuracy (QUADAS-2) tool.

Additional outcome(s) No.

Data management Endnote.

Quality assessment / Risk of bias analysis The quality assessment and bias analysis were completed using the QUADAS-2 and analyzed with Stata.Two investigators independently extract the informations. When the same population was reported in several publications, we retain only the most informative article or the complete study to avoid duplication of information. Any disagreements should be resolved by discussion between the review authors. We will assesse study quality using the modified quality assessment for studies of diagnostic accuracy (QUADAS-2) tool.

Strategy of data synthesis We will estimate the overall sensitivity (SEN) and specificity(SPE) with 95% confidence intervals (CIs) as the mainoutcome measures by using a bivariate regression approach, and constructe summary receiveroperating characteristic (SROC) curves. This approachis based on bivariate mixed effects models, accounts for potential between-study heterogeneity and incorporates the possible correlation between the SEN andthe SPE. By using the pooled SEN and SPE, we will also calculated positive and negative likelihood ratios(PLR and NLR, respectively). We will assess statistically significant heterogeneity using p values and I^2 statistics. When the p value was > 0.1, we considere the data to have no obvious heterogeneity. If the pvalue was < 0.1, we considered the data to have low heterogeneity with I^2 < 25%, moderate heterogeneity when 25% < I^2 50%. Potential between-study heterogeneity will be explored using subgroup analyses. Meta-analysis was performed using Stata.

Subgroup analysis We will conduct subgroup analyses based on severity of illness, different diagnostic criteria.Potential between-study heterogeneity will also be explored using subgroup analyses.

Sensitivity analysis We will conduct sensitivity analysis by sequentially excluding studies. When the model stability is poor, we will identify the literature that contributes to the instability and assess its reasonableness; subgroup analysis will also be attempted. If the included studies have no significant impact on the results, we will use a funnel plot to evaluate the potential publication bias of the included literature.

Language restriction No language restriction.

Country(ies) involved China.

Other relevant information No.

Keywords biomarker, urine, Alzheimer-associated neural thread protein (AD7c-NTP), mild cognitive

impairment, amnestic mild cognitiveimpairment, Alzheimer's disease(AD).

Dissemination plans The target audience：the academic community. Dissemination method: Journal publication. We hope it can contribute to the development of diagnostic methods for Alzheimer's disease.

Contributions of each author

Author 1 - Zhicheng Yan - Author 1 drafted the manuscript .He participate in the guidance and inspection of various stages and complete the writing of the final paper.
Email: yzc556600@qq.com
Author 2 - LeLe Tian - The author extract data and provided statistical expertise.
Email: 3163962963@qq.com
Author 3 - AnZhi Dong - The author extract data and contributed to the development of the selection criteria, and the risk of bias assessment strategy.
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