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AI-Based Tool for Early Diagnosis and Progression Prediction in Alzheimer's Disease: A Multicenter Validation Study

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INTRODUCTION

Alzheimer's disease (AD) is the most common cause of neurodegenerative dementia and poses a major healthcare challenge worldwide. Despite the availability of biological biomarkers, their application in routine clinical settings remains limited. Recent recommendations from eleven European scientific societies and Alzheimer Europe propose a patient-centered diagnostic workflow for memory clinics [1]. Within this context, artificial intelligence (AI) may offer valuable support for clinical staging and diagnosis based on widely available neuropsychological and MRI data [2-3].

OBJECTIVES

This study aimed to evaluate the clinical performance of TRACE4AD™, a CE-marked AI-based medical device, in supporting memory clinics during key diagnostic steps, specifically by assessing its ability to correctly stage cognitive decline, to classify clinical syndromes and formulate causal hypotheses (distinguishing AD from non-AD profiles), and to predict conversion to AD dementia within 24 months.

METHODS

A total of 797 subjects were enrolled from 66 centers (Italy, US, Canada). All underwent 3D T1-weighted MRI and a detailed neuropsychological battery assessing multiple cognitive domains [4]. In 482 cases, CSF biomarkers (Aβ42, t-tau, p-tau) and/or [^{18}F]FDG PET imaging were available [5]. TRACE4AD™ automatically analyzed imaging and cognitive data using an ensemble of Support Vector Machines (SVMs), with feature selection via Principal Component Analysis (PCA) and Fisher Discriminant Ratio (FDR) [6-7]. Clinical performance was assessed in terms of agreement with expert clinical staging (Cohen's kappa), diagnostic accuracy against biomarker-based classification for syndrome identification, and predictive accuracy of conversion to AD dementia at 24 months using clinical follow-up as reference.

RESULTS

TRACE4AD™ showed substantial to almost perfect agreement with clinical staging (κ=0.81 for HS/SCI/WW, κ=0.70 for MCI/MD, κ=0.90 for moderate/severe dementia). In the subset of subjects with biomarker data (n=130), the tool correctly classified AD-related syndromes with 91% accuracy, achieving a positive predictive value of 91% and a negative predictive value of 100%. For prediction of conversion to AD-dementia at 24 months (n=341), TRACE4AD™ reached 89% sensitivity, 82% specificity, 85% overall accuracy, and an AUC of 83%. Furthermore, AI-derived brain volumetric features significantly correlated with CSF biomarkers, particularly in medial temporal regions, and cognitive performance, supporting the tool's biological validity and interpretability.

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CONCLUSIONS

TRACE4AD™ demonstrated high performance in staging, syndrome classification, and prediction of AD conversion, supporting its utility as a statistical and clinical decision-support tool. Its ability to integrate multimodal data in a reproducible, interpretable manner aligns with current intersocietal recommendations [1], providing an innovative and practical solution to enhance early diagnosis and personalized care in memory clinics.

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