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RESEARCH ARTICLE

Mild cognitive impairment-to-Alzheimer's dementia progression risk: the contribution of the *Interceptor* project

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Abstract

BACKGROUND: Mild cognitive impairment (MCI) is an intermediate stage between normal and pathological brain aging, with 30% to 50% progressing to dementia within 3 to 5 years. Early identification of individuals at high risk of progression is crucial for public health strategies.

METHODS: The INTERCEPTOR project included 398 MCI individuals. Baseline assessment included harmonized procedures for sociodemographic, clinical, neuropsychological, genetic (apolipoprotein E), cerebrospinal fluid (amyloid beta tau), electroencephalogram (brain connectivity), magnetic resonance imaging (hippocampal volumetry), and fluorodeoxyglucose positron emission tomography. The baseline and

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follow-up were completed by 351 individuals with MCI with neuropsychological tests every 6 months for 3 years.

RESULTS: Dementia developed in 104 individuals (29.6%), including 85 (22.4%) who met core clinical criteria for probable and possible Alzheimer's disease dementia. A Cox model combining clinical and sociodemographic data achieved a concordance index of 72%, which increased to 82% when neuropsychology and biomarkers were added.

DISCUSSION: The INTERCEPTOR nomogram represents a tool for predicting dementia progression risk, supporting public health strategies, including screening for risk assessment and risk/benefit ratio in innovative treatments.

KEYWORDS
Alzheimer's disease, biomarkers, dementia, mild cognitive impairment, nomogram, prognostic model, public health strategies, risk stratification

Highlights

- Most existing MCI prognostic models rely on retrospective, non-procedure-harmonized datasets with limited real-world applicability.
- The INTERCEPTOR project used a multicenter, harmonized, multimodal approach to predict MCI-to-dementia progression over 3 years, with clinical and neuropsychological evaluation confirmed independently by two clinical experts blinded with respect to the biomarker's findings.
- Multimodal models increased prediction accuracy from 72% (clinical/sociodemographic/neuropsychological only) to 82%, outperforming any single biomarker.
- The INTERCEPTOR nomogram offers flexible, scalable risk stratification, ready for validation and public health implementation.

1 | BACKGROUND

Dementia is a global public health priority (World Health Organization and Alzheimer's Disease International, with an estimated annual cost of one trillion USD.[1] In Italy, approximately 1,200,000 people are living with dementia, generating nearly €23 billion in annual costs.[2] Mild cognitive impairment (MCI) represents a preclinical phase characterized by objective cognitive difficulties that do not impact daily functioning.[3] MCI subjects have a markedly higher risk of progressing to dementia than cognitively unimpaired individuals, with 30% to 50% converting within 3 to 5 years.[4,5] In a recent meta-analysis[5] of 66 clinical-based studies assessing the risk of conversion from MCI to all-cause dementia, the cumulative risk of conversion was 41.5% (95% confidence interval [CI]: 38.3% to 44.7%, I^2 95.5%). No outliers were identified among the included studies. The annual conversion rate (ACR) to all-cause dementia was 10.9% (95% CI: 9.7% to 12.1%, I^2 98.4%) and varied according to the length of follow-up −13.1% (95% CI: 11.1% to 15.2%) in the 3-year follow-up, 11.5% (95% CI: 10.1% to 13.0%) in 3.1 to 5 years, and 7.8% (95% CI: 6.7% to 9.0%) > 5-year follow-up studies. Such an epidemiological review makes it clear that about half or even more of the MCI population does not progress to dementia during the time of follow-up.

Stratifying dementia risk within the MCI population is therefore essential for public health strategies for interventions targeting modifiable risk factors and enhance protective lifestyles. Moreover, disease-modifying therapies for Alzheimer's disease (AD) appear to be more effective during the MCI stage, but they have high direct/indirect costs and may cause serious side effects. This opens a debate on restricting their use to high-risk MCI for clinically and biologically defined AD.[6] Within this frame, the Italian Medicine Agency (AIFA) and Ministry of Health launched the INTERCEPTOR project in March 2018, which was designed to develop a model for stratifying risk of progression from MCI to clinically defined AD. The project does not aim at the definition of a diagnostic pathway but was conceived as a tool for early detection and risk stratification to inform public health policy, optimize resources, including those for disease-modifying drugs, and support preventive care pathways within the National Health System. INTERCEPTOR is a multicenter, 3-year follow-up study that integrates clinical, neuropsychological, and instrumental biomarkers. The study was designed to reflect real-world clinical practice, where biomarker

assessments are not routinely performed at baseline. Participant inclusion was based solely on the core clinical criteria for diagnosing MCI,[7] in accordance with recommendations from the National Institute on Aging–Alzheimer's Association (NIA-AA) workgroups on diagnostic guidelines for AD. Biomarkers most commonly reported in the literature and available in real-world settings at the time the study began were collected within 2 months from recruitment. The primary aim was the development of an innovative tool for stratifying the risk of progression to dementia in a clinically defined MCI population. Secondary aims included assessing the cost-effectiveness, accessibility, and invasiveness for a scalable and equitable early detection framework. The follow-up period was in December 2023, followed by a data quality review and analysis according to the pre-published statistical plan.[8] Protocol details and baseline findings have been reported previously[9,10].

Several studies and databases have addressed aims similar to those of INTERCEPTOR, but with important differences. Australian Imaging, Biomarkers and Lifestyle study and the Alzheimer's Disease Neuroimaging Initiative (ADNI) were primarily research-driven cohorts for biomarker validation, aimed at characterizing amyloid deposition, neurodegeneration, and cognitive trajectories rather than clinically actionable prognostic models.[11]

ADNI emphasized standardized biomarker pipelines for clinical trials. Mayo Clinic Study of Aging (MCSA) was conceived as an epidemiological study to estimate lifetime and 10-year population-level risks of cognitive impairment across biological severity levels, rather than individual clinical prediction tools.[12]

The US National Institutes of Health (NIH)-funded Alzheimer's Disease Research Centers contribute standardized clinical data to the NACC database, and two studies applied machine learning methods to non-invasive variables to develop Excel-based calculators estimating progression risk.[13,14] None of them produced prognostic models for routine clinical practice. The INTERCEPTOR project uniquely fills this gap as a real-world, public health–oriented cohort, enrolling consecutive MCI, with blinded diagnostic outcomes and a primary focus on progression risk stratification.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional sources (e.g., PubMed) to evaluate existing prognostic models for the conversion from MCI to Alzheimer's dementia. Most prior research relied on retrospective datasets, limiting their generalizability. Furthermore, many studies use heterogeneous biomarkers, whereas our study evaluated a comprehensive set of neuropsychological assessments, CSF, ApoE, EEG, MRI, and FDG-PET within a harmonized procedure within a real-world clinical framework.
2. **Interpretation**: Our findings showed the importance of a predictive model capable of flexibly stratifying MCI individuals into risk categories, enabling implementation even in settings with limited access to high-cost biomarkers.
3. **Future directions**: External validation of the INTERCEPTOR nomogram in diverse populations is essential to confirm generalizability. Future research should explore the incorporation of emerging new biomarkers while also investigating protective factors in biomarker-positive patients who remain cognitively stable ("resilient MCI"). Early identification of high-risk MCI individuals may facilitate timely, targeted interventions to delay or prevent dementia onset.

2 | METHODS

A total of 494 participants aged 50 to 85 years, with amnestic (aMCI) and non-amnestic MCI (naMCI) were consecutively screened across 19 Italian memory clinics between January 2019 and October 2020, with recruitment extended due to the COVID-19 pandemic. The memory clinics, selected through a public call, were distributed throughout Italy, from the North to the South. The participating centers included a mix of university hospitals and regional memory units, which collectively cover a broad spectrum of clinical settings. MCI diagnosis followed criteria from the NIA-AA[7]: Mini-Mental State Examination (MMSE) score > 24/30 (age/education-corrected); Clinical Dementia Rating (CDR) scale = 0.5; cognitive complaints; deficits in at least one cognitive domain; and preserved global functioning. A full list of exclusion and inclusion criteria is reported in the Table S1. At baseline, clinical, sociodemographic, and neuropsychological data were collected. Within 60 days, the following a priori planned biomarkers were obtained: MMSE, Delayed Free Recall DFR from the Free and Cued Selective Reminding Test (FCSRT), fluorodeoxyglucose positron emission tomography (FDG-PET) for brain glucose metabolism, 3D T1 MRI for hippocampal volumetry, electroencephalogram (EEG) (graph theory metrics) for brain connectivity, apolipoprotein E (apoE) genotype, and cerebrospinal fluid (CSF) biomarkers (amyloid beta [Aβ] 42, Aβ42/Aβ40, total tau [t-tau], tau phosphorylated at threonine 181 [p-tau181], Aβ42/p-tau181). The study employed a "hub and spoke" organizational model, with recruiting centers (spokes) responsible for subjects' enrollment and expert centers (hubs) in charge of biomarker examination and risk diagnosis.

2.1 | Biomarkers

Biomarkers were selected due to their established or emerging relevance in the literature published up to 2017 in the characterization of AD, as well as their ability to capture complementary aspects of brain structure, function, and pathology.

2.1.1 | Neuropsychological biomarkers

For neuropsychological biomarkers two tools were chosen: the MMSE,[15] which is one of the most widely used short screening tool for assessing overall cognitive impairment in clinical setting,[16] and the FCSRT, an episodic memory test based on semantic cueing developed with the specific aim of identifying patients with amnestic syndrome of the medial temporal type. This test has proven effective in differentiating individuals in the early stages of AD from those with MCI who do not progress to dementia.[17,18]

2.1.2 | Cerebrospinal fluid biomarkers

CSF samples were collected in the morning by lumbar puncture, centrifuged at 2000 × g for 10 min within 1 h from collection, aliquoted in 500 μL polypropylene tubes (Sarstedt), stored at −80°C, and shipped on dry ice to the expert center for the analysis. Aβ40, Aβ42, t-tau and p-tau181 were measured via fully automated chemiluminescence enzyme immunoassay (CLEIA) and the Lumipulse G600II instrument (Fujirebio) with the kits Lumipulse G β-Amyloid 1-40 (lot number 4072), Lumipulse G β-Amyloid 1-42 (lot number 4121), Lumipulse G Total Tau (lot number 4063), and Lumipulse G pTau181 (lot number 4074) (Fujirebio). The following normative limits were used: Aβ42 ≥ 640 pg/mL, Aβ42/Aβ40 ≥ 0.068, t-tau ≤ 404 pg/mL, p-tau181 ≤ 56 pg/mL, Aβ42/p-tau 181 ≥ 11.8.[19–23] The quality controls (QCs) were provided by the manufacturer and were measured at the beginning of each analytic session with an inter-run variation of <6%.

2.1.3 | Fluorodeoxyglucose positron emission tomography

The 18F-FDG-PET was acquired with a 3D scanner followed by a voxel-based single-subject analysis using the optimized statistical parametric mapping procedure with a large database of normal controls for comparison and a FDG atlas for image normalization.[24,25]

2.1.4 | APOE ε4 genotype

For the ApoE ε4 genotype, DNA was extracted from peripheral blood samples according to standard procedures. ApoE genotyping[26] was performed by the expert center using polymerase chain reaction-amplification of exon 4 spanning both polymorphic codons, followed by direct Sanger sequencing of the amplification products (forward primer: 5'-GCCTACAAATCGGAACTGGA-3'; reverse primer: 5'-CGCCACCTGCTCCTTCACCT-3'

2.1.5 | Electroencephalogram

For the computation of EEG brain connectivity, 19 scalp electrodes were positioned according to the International 10–20 System, along with electrooculography channels. Skin–electrode impedances were maintained below 5 KΩ, and the sampling rate was set at 256 Hz. The EEGs were preprocessed by removing artifacts, and connectivity was analyzed using eLORETA, computed across 84 regions of interest (ROIs) (42 Brodmann Areas [Bas] per hemisphere).[27] The intracortical lagged linear coherence (LLC) was calculated for all possible pairs of the 84 ROIs within each of the seven EEG frequency bands, namely, delta (2 to 4 Hz), theta (4 to 8 Hz), alpha 1 (8 to 10.5 Hz), alpha 2 (10.5 to 13 Hz), beta 1 (13 to 20 Hz), beta 2 (20 to 30 Hz), and gamma (30 to 45 Hz), for each subject. LLC measured connectivity in the EEG frequency bands. Networks were built with BAs as nodes and LLC as edges. Weighted and undirected brain networks were constructed using the Brain Connectivity Toolbox, adapted into MATLAB scripts, with cortical sources estimated in the BAs serving as vertices and the edges weighted using the LLC values between each pair of vertices. The small world (SW) parameter evaluated brain network organization, computed as the ratio of clustering coefficient (Cw) to path length (Lw), normalized across EEG frequency bands.[27] The SW index was determined by calculating the ratio of the normalized clustering coefficient to the normalized characteristic path length for all EEG frequency bands. It has been demonstrated that AD alters all EEG frequency bands; therefore, a suitable approach appears to be the combination of the seven frequency-specific SW parameters into a single index instead of selecting a single band or a subset. Accordingly, a single SW-derived index, SWcomb, was computed by combining the seven SW parameters from each frequency band (Table S2). To decrease the number of degrees of freedom, the seven EEG frequency parameters were combined into a single index using the Constrained Optimization by Linear Approximation (COBYLA) algorithm, which was applied to find the optimal combination of parameters capable of maximizing the discriminative power between AD and healthy subjects. COBYLA iteratively explores different combinations of feature weights while adhering to predefined constraints, such as the need to preserve the original EEG information. The resulting composite index enhances the accuracy, sensitivity, specificity, and effectiveness of AD diagnosis.

The SWcomb index is defined as

$$SW_{comb} = w_{\delta} * SW_{\delta} + w_{\theta} * SW_{\theta} + w_{\alpha 1} * SW_{\alpha 1} + w_{\alpha 2} * SW_{\alpha 2} + w_{\beta 1} * SW_{\beta 1} + w_{\beta 2} * SW_{\beta 2} + w_{\gamma} * SW_{\gamma}$$

where the coefficients for each frequency band are reported in Table S2.

Thereafter, each SW parameter was standardized using the mean and standard deviation (Supplementary Table 2) derived from AD and healthy populations, then weighted according to the coefficients established by Vecchio et al.[28] The EEG parameter SWcomb was analyzed in both continuous and categorized forms. To classify values in normal/abnormal, a fine Gaussian support vector machine (SVM) was employed using the SW index. The adopted machine learning algorithm had been previously trained on external data including both healthy subjects and patients with AD.[28]

2.1.6 | Magnetic resonance imaging

High-quality volumetric T13D images, ensured by compliance with MRI Standard Operating Procedures (SOP), were acquired at 1.5T or 3T with 1 mm isotropic voxels and were archived in XNAT according to Digital Imaging and COmmunications in Medicine (DICOM or Neuroimaging Informatics Technology Initiative (NIFTI) standards. All collected scans were evaluated using MRI-QC software[29] based on the quality metrics with signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR). Hippocampal volumetry was determined with two algorithms: (i) FreeSurfer version 6.0,[30] which uses the subject-probabilistic atlas of the Center for Morphometric Analysis, and (ii) the ACM AdaBoost algorithm[31] used for the segmentation of the hippocampal region according to the Harp protocol.[32] The hippocampal volumes determined with the two algorithms were related to the subject's space and normalized in relation to the total intracranial volume (TIV). The volumes were expressed in cubic millimeters, and the results, quality controlled by two experienced neuroimagers (AR, SDF), were contrasted against the scientifically validated normative curves of the Italian population.[32] For the definition of abnormalities in hippocampal volumetry, a cut-off value below the fifth percentile was used. The age-specific reference cut-offs are provided in previous publications.[8,32]

2.1.7 | Harmonizazion procedures and conversion diagnostic criteria

Extensive harmonization procedures were implemented at the beginning of the project, including both in-person and remote training sessions during the first 3 months, to ensure consistency in clinical, neuropsychological, and sociodemographic data and biomarkers collection across all 19 participating memory clinics.

Throughout the study – at enrollment, during follow-up visits, and at the time of dementia conversion – data quality was closely monitored and centrally validated by the study coordinating team. In fact, approximately the final 10 months of the study were dedicated exclusively to verifying and re-verifying data quality across centers.

Data were pseudo-anonymized and uploaded to a web platform (XNAT); CSF and blood samples were sent to a central laboratory. Details on the organizational architecture of the study and biomarkers' acquisition are provided in a previous publication.[9] Subjects were followed every 6 months for up to 36 months with neuropsychological and neurological assessments.

In line with international guidelines, the diagnosis of probable and possible AD dementia was based only on clinical criteria, specifically those proposed by the NIA-AA.[33] Reflecting the real-world nature of our sample, biomarker data were not required for the diagnostic process.

At each follow-up visit, conversion to probable and possible AD dementia or other dementia was determined according to clinical criteria.[33–35] The diagnosis was made blinded to the subject's biomarker status and was based on clinicians' assessment, worsening of cognitive/behavioral function, and/or functional status, specifically defined by a MMSE score < 24/30, extensive neuropsychological evaluation, functional decline, neurological evaluation, and CDR = 1 in accordance with Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria. The progression to AD dementia core clinical criteria was proposed by each local memory clinic and then confirmed independently by two clinical experts blinded with respect to the biomarker's findings.

The study spanned 64 months: ~20 months for harmonization/recruitment, 36 months for follow-up, and 8 months for QC (performed by FL, NC, PL) and analysis (performed by FL, PL). Ethical approval was granted by the A. Gemelli University Polyclinic Foundation Ethics Committee (Protocol 37756/18 ID: 2251; 27/09/2018).

2.2 | Statistical plan

Analyses were planned in full compliance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidelines[36] and followed the statistical analysis plan (SAP) that has been published elsewhere.[8]

The primary project endpoint was clinical conversion to AD, defined as the time from the first neuropsychological assessment to the date of the last follow-up visit, conversion, or death. The time of conversion was set at the first visit with a diagnosis of dementia if confirmed in the following visit. Other forms of dementia were classified as non-conversion in order to analyze the entire predefined cohort in accordance with the study design and to avoid introducing selection bias.[37] A multivariable prediction model was developed using a Cox regression analysis in two steps:

(i) Pre-identified sociodemographic and clinical factors associated with dementia were analyzed (Table 1). As per SAP, single imputation by chained equations was applied to clinical and demographic variables due to the limited amount of missing data (less than 5%). Due to the small number of imputed data (only 11 records with at least one missing value among clinical factors), this may be considered an acceptable approach to address missing data[38,39] and it is not expected to inflate the precision of the estimates. Variable selection used a stepwise backward procedure with a removal threshold of 0.10 and a re-entry threshold of 0.05. This defined the base model.
(ii) Biomarkers were analyzed and included in the stepwise selection procedure to develop the full prediction model. Candidate variables included the clinical variables from the base model along with all biomarker-related parameters. No imputation was performed for missing values; therefore, the evaluation of each biomarker utilized all data available for the specific biomarker (Figure S1). This approach was considered acceptable because the number of missing values for each biomarker was expected to be limited, and the missing data mechanism could reasonably be assumed missing at random. Indeed, missingness was primarily attributable to logistical and operational issues (inadequate or lost biological samples,

TABLE 1 Characteristics of participants by conversion to AD dementia.

	Overall $N = 351$	Converting to AD dementia $N = 85$	Not converting to AD dementia $N = 266$*	*p* value
Demographic-clinical variables				
Gender, *n* (%)				
Female	182 (51.9%)	55 (64.7%)	127 (47.7%)	*0.006*
Male	169 (48.1%)	30 (35.3%)	139 (52.3%)	
Age (years), mean ± SD	71.9 ± 6.9	74.0 ± 6.3	71.2 ± 6.9	*<0.001*
Education (years), mean ± SD	10.6 ± 4.5	10.3 ± 4.5	10.6 ± 4.5	0.577
Type of MCI, *n* (%)				
Amnesic single domain	176 (50.1%)	46 (54.1%)	130 (48.9%)	0.838
Amnesic multidomain	138 (39.3%)	31 (36.5%)	107 (40.2%)	
Non-amnesic single domain	21 (6.0%)	5 (5.9%)	16 (6.0%)	
Non-amnesic multidomain	16 (4.6%)	3 (3.5%)	13 (4.9%)	
MCI diagnosis, *n* (%)				
Incident	276 (78.6%)	62 (72.9%)	214 (80.5%)	0.141
Prevalent	75 (21.4%)	23 (27.1%)	52 (19.5%)	
Amsterdam IADL, mean ± SD	8.2 ± 10.9	13.2 ± 14.2	6.6 ± 9.0	*<0.001*
CIRS severity, mean ± SD	1.3 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	0.389
CIRS comorbidity, *n* (%)				
0	208 (60.5%)	50 (61.0%)	158 (60.3%)	0.928
1	84 (24.4%)	22 (26.8%)	62 (23.7%)	
2	31 (9.0%)	6 (7.3%)	25 (9.5%)	
3	16 (4.7%)	3 (3.7%)	13 (5.0%)	
4/5	5 (1.5%)	1 (1.2%)	4 (1.5%)	
Family history of dementia				
No	188 (53.9%)	36 (42.9%)	152 (57.4%)	*0.020*
n (%)				
Yes	161 (46.1%)	48 (57.1%)	113 (42.6%)	
Smoke, *n* (%)				
No	221 (63.1%)	62 (72.9%)	159 (60.0%)	*0.031*
Yes/ex-smoker†	129 (36.9%)	23 (27.1%)	106 (40.0%)	
Cohabitation, *n* (%)				
No	54 (15.5%)	12 (14.5%)	42 (15.8%)	0.770
Yes	295 (84.5%)	71 (85.5%)	224 (84.2%)	
Physical activity, *n* (%)				
No	241 (69.1%)	71 (83.5%)	170 (64.4%)	*<0.001*
Yes	108 (30.9%)	14 (16.5%)	94 (35.6%)	0.980
Hypertension, *n* (%)				
No	159 (46.2%)	38 (46.3%)	121 (46.2%)	
Yes	185 (53.8%)	44 (53.7%)	141 (53.8%)	0.304
Cardiovascular disease, *n* (%)				
No	230 (66.9%)	51 (62.2%)	179 (68.3%)	
Yes	114 (33.1%)	31 (37.8%)	83 (31.7%)	
Psychiatric disease, *n* (%)				
No	234 (68.0%)	54 (65.9%)	180 (68.7%)	0.629
Yes	110 (32.0%)	28 (34.1%)	82 (31.3%)	

(Continues)

TABLE 1 (Continued)

	Overall $N = 351$	Converting to AD dementia $N = 85$	Not converting to AD dementia $N = 266$*	*p* value
Biomarkers				
MMSE, mean ± SD	25.9 ± 2.3	24.7 ± 2.0	26.3 ± 2.3	*<0.001*
DFR, mean ± SD	4.9 ± 3.8	2.9 ± 3.3	5.6 ± 3.7	*<0.001*
APOE ε4, *n* (%)				
Non carrier	197 (59.7%)	42 (51.9%)	155 (62.2%)	0.095
Heterozygote	114 (34.5%)	31 (38.3%)	83 (33.3%)	
Homozygote	19 (5.8%)	8 (9.9%)	11 (4.4%)	
CSF, mean ± SD				
Aβ42, pg/ml	713.3 ± 383.2	567.2 ± 330.5	762.4 ± 387.8	*<0.001*
total tau, pg/ml	474.3 ± 316.8	612.1 ± 305.6	427.8 ± 307.4	*<0.001*
p-tau 181, pg/ml	73.1 ± 54.2	97.8 ± 52.7	64.7 ± 52.2	*<0.001*
Aβ42/Aβ40 ratio	0.07 ± 0.03	0.05 ± 0.02	0.07 ± 0.03	*<0.001*
Aβ42/p-tau 181 ratio	16.6 ± 14.0	8.9 ± 9.4	19.2 ± 14.3	*<0.001*
Hippocampal volume, mean ± SD				
FS right, mm^3	3162.1 ± 462.4	2960.0 ± 441.9	3227.9 ± 450.5	*<0.001*
FS left, mm^3	3046.4 ± 444.3	2845.3 ± 435.5	3111.1 ± 428.2	*<0.001*
AA right, mm^3	4754.2 ± 586.5	4548.2 ± 648.1	4821.5 ± 549.6	*<0.001*
AA left, mm^3	4555.5 ± 645.8	4268.9 ± 690.2	4650.0 ± 602.6	*<0.001*
FDG-PET, *n* (%)				
Non-AD-like	201 (59.6%)	31 (38.8%)	170 (66.1%)	*<0.001*
AD-like	136 (40.4%)	49 (61.3%)	87 (33.9%)	
Non-pathological	67 (19.9%)	4 (5.0%)	63 (24.5%)	*<0.001*
Pathological	270 (80.1%)	76 (95.0%)	194 (75.5%)	
EEG SW, mean ± SD				
Delta	1.003 ± 0.015	1.001 ± 0.014	1.004 ± 0.015	0.060
Theta	1.008 ± 0.012	1.003 ± 0.012	1.009 ± 0.011	*<0.001*
Alpha1	0.993 ± 0.011	0.994 ± 0.012	0.993 ± 0.011	0.624
Alpha2	0.995 ± 0.013	0.999 ± 0.014	0.994 ± 0.012	*0.010*
Beta1	1.010 ± 0.013	1.011 ± 0.013	1.010 ± 0.013	0.227
Beta2	1.014 ± 0.014	1.014 ± 0.014	1.014 ± 0.014	0.827
Gamma	1.006 ± 0.019	1.004 ± 0.018	1.006 ± 0.019	0.372
SW combined	1.7 ± 20.9	9.5 ± 24.0	−0.8 ± 19.2	*<0.001*

Abbreviations: AA, ACM AdaBoost; AD, Alzheimer's disease; CIRS, Cumulative Illness Rating Scale; DFR, Delayed Free Recall; EEG, electroencephalogram; FDG-PET, fluorodeoxyglucose positron emission tomography; FS, FreeSurfer; IADL, instrumental activities of daily living; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SD, standard deviation; SW, small world.
*Includes non-converters and converters to other forms of dementia.
†Current smokers are only 22 (6.3%) of the overall population, 7.5% among non-converters to AD and 2.4% among AD converters.

technical problems in uploading MRI images to the centralized web platform, artifacts affecting the interpretation of FDG-PET scans). The final model was developed on the subset of participants for whom all the biomarkers selected were available.

In both steps, collinearity was evaluated using the variance inflation factor (VIF), the proportional assumption was checked, and variable transformations were evaluated to address non-linearity. However, for no biomarkers was a violation of linearity was observed. Biomarkers were evaluated individually and in terms of their added value to the base model, considering both continuous and categorical forms, except for ApoE ε4 and FDG-PET metabolic patterns (AD-like, non-AD-like), which were analyzed only categorically. Categorization was based on literature reference cut-offs as outlined in the SAP.[8] In

addition, optimal cut-offs were determined within this MCI cohort using the corrected values (Table S2) based on the nearest 1-to-0 method. The predictive performance of each categorical biomarker was assessed through sensitivity, specificity, positive and negative likelihood ratio (LR), and positive and negative predictive values (PPV and NPV). The additional contribution of each biomarker beyond the base model was assessed for the continuous and categorical (based on both reference and data-driven cut-offs) forms using the delta C-index, LR test, Akaike information criterion (AIC), and the category-free net reclassification improvement (NRI) reported overall and separately for cases and non-cases. For the prediction model development, biomarkers were considered in their continuous form. After stepwise selection, simplification of the full model to a reduced model was considered, following Harrell's recommended strategy for prediction model development.[40] In addition, the incorporation of external evidence and background knowledge into variable selection is particularly recommended in the context of small sample sizes, as it improves the stability and overall quality of prognostic models.[40–42] Accordingly, correlations among variables were evaluated to avoid redundancy, and selected predictors were further assessed based on their consistency with the existing literature. Changes in the C-index were examined, and agreement between the full model (considered the reference model) and the refined model was evaluated by regressing the prognostic indices of the two models. In line with methodological recommendations, a coefficient of determination (R^2) of at least 0.95 was considered indicative of adequate agreement. For the final model, performance was evaluated using Harrell's C-statistics for discrimination, calibration plot based on individual event probabilities,[43] calibration slope and calibration intercept, scaled Brier score, and Nagelkerke's R^2 modified version.[44] Internal validation was performed to provide an over-optimism adjusted C-index and calibration slope,[36,40] which was used as a shrink factor to recalibrate the model. Internal validation was performed using 500 bootstrap samples, following Harrell's steps and including the modeling selection procedure.[40] The model was visualized using a nomogram,[45] providing both a graphical and manual tool for calculating the 3-year risk of conversion to AD. Several percentiles of the predicted conversion probability at 3 years were evaluated in terms of sensitivity, specificity, and PPV. Finally, low-, medium-, and high-risk groups were defined based on quartiles of predicted progression-to-dementia probabilities, with the first and second quartiles combined for the low-risk category. The high-risk threshold was chosen to balance sensitivity and PPV.

2.2.1 | Subgroup analysis

In light of the recent approval of lecanemab (LEQEMBI), an amyloid-targeting monoclonal antibody for the treatment of AD, by the European Medicines Agency (EMA), the prediction model was applied to the subgroup of participants fulfilling the indications for treatment with lecanemab, specifically, Aβ-positive individuals (Aβ42/p-tau181 $\leq$ 11.8 or Aβ42/40 $\leq$ 0.068) without ApoE ε4 homozygosity. The performance of the model was then evaluated in this subset. This analysis was not planned in the SAP.

2.2.2 | Sensitivity analyses

To develop the prediction model, a required sample size of 500 participants was estimated in order to achieve 400 persons fully evaluated.[8] Due to the pandemic, this target was not reached, and 351 participants, with a total of 85 AD events, were included in the analysis. We acknowledge that developing a predictive model with a limited number of events relative to the number of candidate variables increases the risk of bias.[41] To assess the robustness of biomarker selection, several sensitivity analyses were performed.[41,46] The stepwise procedure was repeated with varying p value thresholds for removal and re-entry, including the AIC. Additionally, the Least Absolute Shrinkage and Selection Operator (LASSO) method was applied in combination with the backward elimination.[47] To evaluate the impact of having censored the conversion to other forms of dementia in the main analysis, the competing event analysis was applied using Fine and Gray's semi-parametric proportional sub-distribution hazards model. The analysis was repeated considering also death as competing events.

Furthermore, as 50 participants had at least one missing biomarker, we compared the clinical characteristics of participants with complete data with those of participants with incomplete data. In addition, we repeated the main analysis using multiple imputation by chained equations to impute missing biomarker values, in order to assess the potential bias introduced by the complete-case analysis. Biomarkers were imputed using 15 imputations, corresponding to the overall proportion of missing data. Logistic regression was applied for the categorical ApoE ε4 variable, while predictive mean matching with five nearest neighbors was used for continuous biomarkers. The imputation model included the risk factors selected in the initial step, the outcome variable, the censoring indicator, and the cumulative baseline hazard function estimated using the Nelson–Aalen method and biomarkers.

2.2.3 | Additional analysis on COVID-19

Enrollment was still ongoing when the COVID-19 pandemic emerged. By the time it was declared (March 11, 2020), 71.2% of participants had already been recruited, while the remaining 28.8% were enrolled during the pandemic period under partial lockdown measures (after June 1, 2020). An analysis was conducted to assess whether this event influenced participant selection. Descriptive statistics were provided for participants grouped according to the enrollment period to evaluate possible selection bias due to the pandemic. Moreover, COVID-19 infection was included as a time-dependent covariate in the model.

Significance was set at 5%. Analyses were performed using Stata version 18.0 (StataCorp, College Station, TX, USA) and R software version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

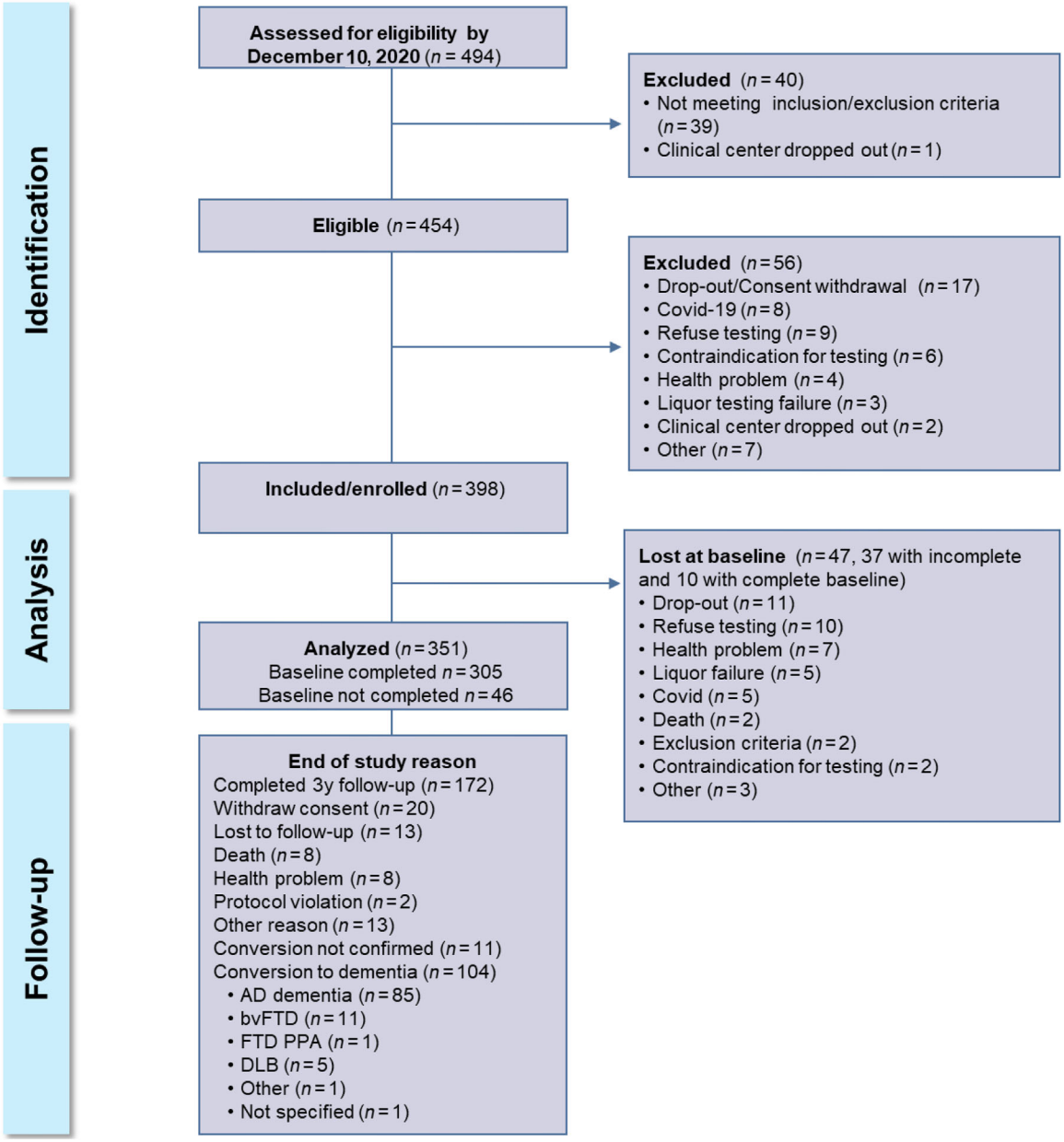

FIGURE 1 Study flowchart. AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; FTD PPA, frontotemporal dementia primary progressive aphasia; DLB, dementia with Lewy bodies.

3 | RESULTS

A total of 494 individuals were screened for eligibility, of whom 454 met the inclusion criteria; of these, 398 participants were enrolled (reasons for exclusion are reported in the study flowchart; Figure 1); 47 participants (11.8%) were lost at baseline.

Overall, 351 participants were included in the final analysis (see Table 1 for demographic and clinical characteristics, along with all biomarker parameters at baseline). A list of protocol deviations is provided in Table S3, and a detailed description, including the neuropsychological assessment, is presented in Table S4.

During follow-up, 85 participants (24.2%) converted to probable and possible AD dementia (AD converters), according to the core clinical criteria.[33] An additional 19 participants (5.4%) progressed to other clinically defined forms of dementia, most commonly the behavioral variant of frontotemporal dementia (Figure 1), resulting in a total conversion risk of 29.6%. For this study, we refer to non-converters to AD ($n = 266$) as individuals with MCI who either remained cognitively stable ($n = 247$) or converted to non-AD dementias. This grouping reflects a comparison framework specifically focused on the progression to clinically defined AD dementia. The mean follow-up duration was 2.3 years (range: 0.5 to 4.2 years), with a mean of 1.4 years for AD dementia converters and 2.6 years for non-converters to AD. The AD dementia incidence rate was 12.9 (95% CI: 10.7% to 15.6%) per 100 person-years. Notably, the conversion rate peaked in the second year of follow-up, with a steep decline in the third year and a conversion

rate of 3.1% in the last 6 months. We acknowledge that the proportion of converters could be higher including also patients converted after the established 3-year follow-up. A longer time perspective may lead to modifications of the weight of each marker in defining the risk of conversion from MCI to dementia. However, a follow-up duration up to 3 years, chosen as the endpoint for our project, has been widely used in the epidemiologic literature on MCI progression to dementia.[5]

The stepwise procedure identified the following demographic and clinical characteristics that constituted the base model: gender, age, family history of dementia (in first- or second-degree relatives), and Amsterdam instrumental activities of daily living (IADL) score. The base model showed a C-index of 0.72 (95% CI: 0.66 to 0.78) and an AIC of 893.4. Although physical activity was associated with AD dementia in the univariate analysis[10] (Table 1), it was excluded from the model because the frequency and intensity reported in interviews could not be reliably quantified.

In the AD dementia-converter group, 51.8% had at least four positive biomarkers, compared to 24.9% among non-converters to AD. Figure 2 shows the distribution of participants according to the number and type of positive biomarkers, separated into AD dementia converters and non-converters to AD. Biomarkers' performance was evaluated in both continuous and categorical form. The sensitivity of biomarkers, when categorized using reference cut-offs, ranged from a minimum of 24.7% for MMSE to a maximum of 80.7% for phosphorylated tau (p-tau181) and Aβ42/p-tau181 ratio. Specificity ranged from a minimum of 47.0% for FCSRT-DFR to a maximum of 86.1% for MMSE. The PPV never exceeded 44% (Table 2). Measures of the added value of each biomarker to the base model are reported in Table S5. For all biomarkers, the continuous form outperformed or was equivalent to the reference-based categorical form. In a few cases, the data-driven categorical form (optimal cut-off) performed better than the continuous form (Table 2, Table S5); however, the categorical form was not pursued, as its use is strongly discouraged in the literature,[36,40,48] and the continuous form was preferred for the predictive model development.

The backward stepwise procedure was applied to a full model that included the four risk factors identified in the base model and 13 parameters related to the seven biomarkers. Total tau was excluded a priori due to high collinearity with p-tau181 (VIF > 10). After exclusion of the t-tau, VIFs were recalculated, showing no further problematic collinearity (all VIFs $\leq$ 8.5).

The following covariates were selected: gender, age, family history of dementia, Amsterdam IADL, MMSE, Aβ42/p-tau181 ratio, Aβ42/Aβ40 ratio, right hippocampal volume by FreeSurfer, and EEG SW-combined index.

The model was refined based on the existing literature and in accordance with the principle of parsimony avoiding redundancy. The right hippocampal volume, measured using the FreeSurfer technique, was replaced with the left one, which has greater support in the literature,[49] and the Aβ42/Aβ40 ratio was removed due to its strong correlation with Aβ42/p-tau181 (Table 3a). The final model showed a minimal and non-statistically significant reduction in the C-index (−0.009, DeLong test $p = 0.136$) and a very high level of agreement with the full model ($R^2 = 0.95$); the model was developed using the subset of 323 participants with non-missing biomarker data (Figure S1).

The final model had a C-index of 0.82 (95% CI: 0.78 to 0.86). The AIC was 794.9, the R^2 was 0.75 (95% CI: 0.65 to 0.86), the scaled Brier score was 36.3%, the calibration slope and intercept were 0.04 and 1.01, respectively. The calibration plot showing graphically the individual probability observed and predicted is provided in Figure 3. After internal validation, the optimism-corrected C-index was 0.78 (0.74 to 0.82) and the calibration slope was 0.79 (95% CI: 0.58 to 1.04). The final risk model was recalibrated (Table 3b) and presented as a nomogram in Figure 4.

Based on quartiles of predicted 3-year conversion probabilities, three risk groups were identified: low (recalibrated predicted probability between 0 and 21.9%), medium (between 22% and 43.9%), and high (equal to or above 44%). The cut-off identifying the high-risk group had a sensitivity of 64.2%, specificity of 88.0%, PPV of 64.2%, and overall accuracy of 82.0%.

3.1 | Subgroup analysis

As a proof of principle, the model was applied to participants fulfilling the EMA indication for lecanemab treatment (amyloid-positive without ApoE ε4 homozygosity) comprising 178 individuals (50.7% of the study cohort) and demonstrated good discrimination and calibration performance. The model's discriminative ability for predicting conversion to AD in this subgroup reached a C-index of 0.77 (95% CI: 0.72 to 0.83), with a calibration slope of 1.06 (95% CI: 0.64 to 1.48) and an intercept of 0.006 (95% CI: −0.29 to 0.30) (Figure S2). The R^2 was 0.63 (95% CI: 0.44 to 0.77). The cut-off established for the high-risk group in the primary analysis (3-year conversion probability of 44%) showed a sensitivity of 72.4%, specificity of 79.3%, and a PPV of 63.6%. Applying this threshold, 37.6% of the subgroup was classified as high risk (67 out of 178).

3.2 | Sensitivity analyses

To assess the robustness of biomarkers' selections, the stepwise procedure was repeated using different thresholds for removal and re-admission of variables. As thresholds increased, FDG-PET was added to the selected set (Table S6). However, including FDG-PET in the final model did not significantly improve predictive accuracy (LR test = 0.0647; delta C-index = 0.009 with $p = 0.058$). Additionally, as an alternative method, the LASSO method was applied, and it identified a broader set of variables, adding FCSRT-DFR, ApoE ε4, FDG-PET, Aβ42, and left hippocampal volume (by FS technique) to those already selected in the primary analysis. Applying backward selection after LASSO, the subset of predictors identified in the primary analysis was selected together with an AD-like FDG-PET pattern. Finally, the competing event analysis was performed to assess the impact of censoring conversions to other forms of dementia. When the 19 conversions to other forms of dementia were considered as competing events, the

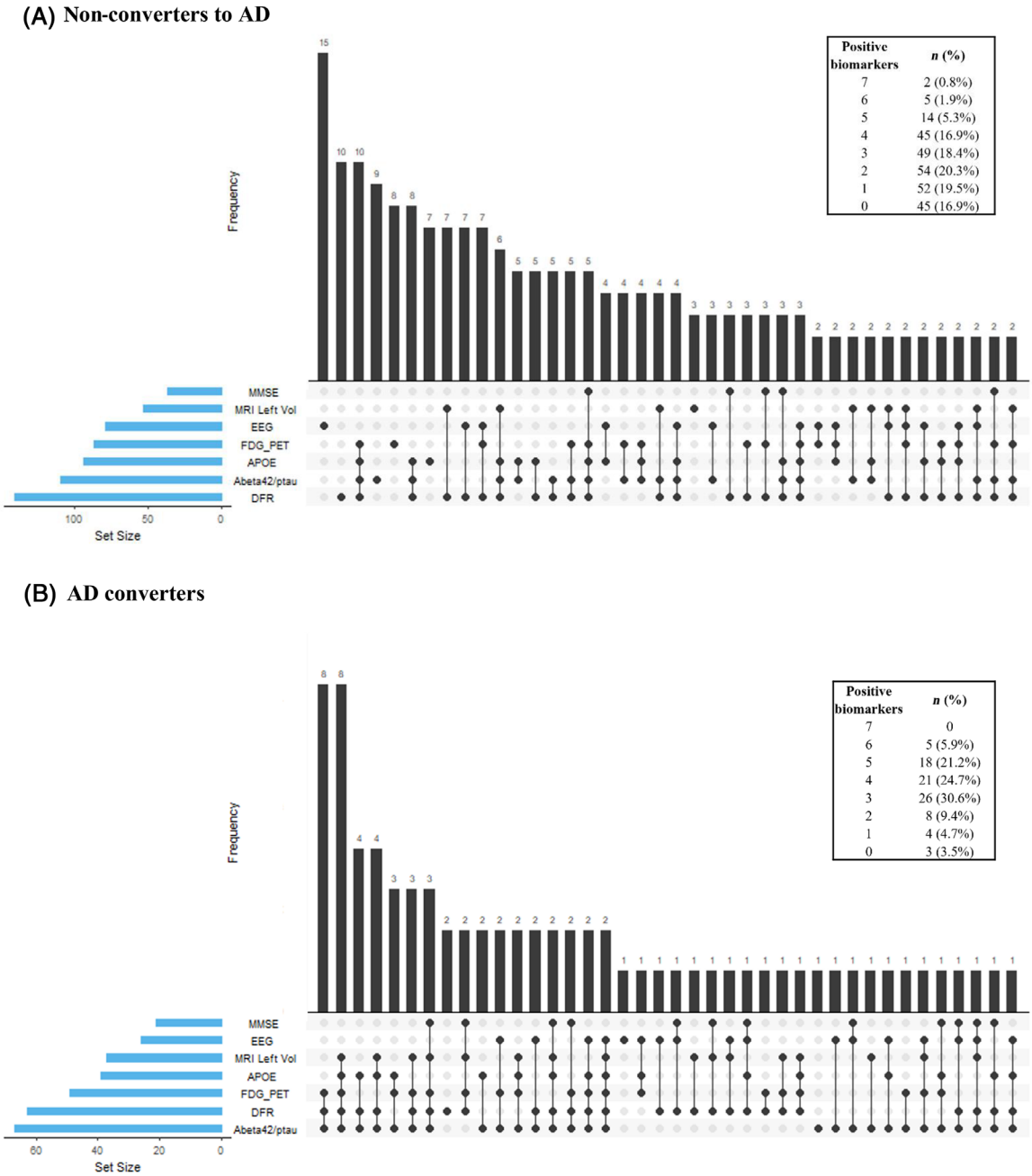

FIGURE 2 Frequency of subjects with each observed combination of positive biomarkers in (A) non-converters to AD and (B) AD converters. Each bar represents the number of subjects with a given biomarker profile. Biomarker positivity is indicated by a black dot.

selected variables remained unchanged. However, FDG-PET was additionally selected when both conversions to other forms of dementia and deaths ($n = 8$) were treated as competing events (Table S7).

To assess the potential bias introduced by the complete-case analysis, we examined the pattern and impact of missing data. We compared the clinical characteristics of participants with complete data ($n = 301$) with those of participants with at least one missing biomarker ($n = 50$). Compared with the incomplete-data group, participants with complete data were younger (mean age 71.6 vs 73.7 years, $p = 0.047$), had a higher level of education (10.8 vs 9.1 years, $p = 0.0125$), and presented fewer comorbidities (36.0% vs 61.7% with Cumulative Illness Rating Scale (CIRS) comorbidity index > 0, $p < 0.001$), although not in terms of the CIRS severity index. No differences were observed in the main neuropsychological test scores.

Finally, we imputed biomarker values and repeated the stepwise selection, within each of the 15 imputed datasets, confirming the set of selected variables in the complete-case analysis (Table S8). The exception was the selection of FDG-PET in only two imputations, without reaching statistical significance. Notably, the Aβ42/Aβ40 ratio was selected in approximately half of the imputations, and left hippocampal volume was selected in about 40% of cases instead of the right hippocampal volume, suggesting that left and right hippocampal mea-

TABLE 2 Diagnostic performance of biomarkers: continuous form and categorized form using reference cut-offs and data-driven optimal cut-offs (*).

	SE	SP	LR+	LR−	PPV	NPV	Accuracy	AUC	HR	*p* value	95% CI	C-index	95%CI
MMSE													
MMSE, per unit									0.75	*0.000*	(0.69, 0.83)	0.70	(0.65,0.75)
MMSE < 24	24.7%	86.1%	1.78	0.87	36.2%	78.2%	71.2%	0.55	2.30	*0.001*	(1.40, 3.77)	0.57	(0.52,0.62)
MMSE ≤ 25.4*	74.1%	63.9%	2.05	0.41	39.6%	88.5%	75.8%	0.69	4.64	*0.001*	(2.85, 7.55)	0.69	(0.64,0.73)
FCSRT DFR													
DFR, per 1 unit									0.82	*0.000*	(0.76, 0.87)	0.72	(0.66,0.77)
DFR ≤ 6.31	74.1%	47.0%	1.40	0.55	30.9%	85.0%	53.6%	0.61	2.64	*0.000*	(1.62, 4.29)	0.62	(0.57,0.66)
DFR ≤ 2.72*	62.3%	71.8%	2.21	0.52	41.4%	85.7%	69.5%	0.67	4.07	*0.000*	(2.62, 6.32)	0.68	(0.63,0.73)
APOE ε4													
Carrier versus non carrier	48.2%	62.2%	1.27	0.83	29.3%	78.7%	58.8%	0.55	1.51	0.066	(0.97, 2.33)	0.55	(0.50,0.61)
CSF													
Aβ42, per 100 pg/mL									0.84	*0.000*	(0.78, 0.91)	0.66	(0.60,0.71)
Aβ42 ≤ 640 pg/mL	73.5%	52.6%	1.55	0.50	34.3%	85.5%	57.9%	0.63	2.83	*0.000*	(1.74, 4.61)	0.62	(0.57,0.67)
Aβ42 ≤ 626 pg/mL*	72.3%	55.1%	1.61	0.50	35.1%	85.5%	59.4%	0.64	2.92	*0.000*	(1.80, 4.72)	0.62	(0.57,0.68)
Total tau, per 100 pg/mL									1.13	*0.000*	(1.07, 1.19)	0.68	(0.62,0.74)
Total tau ≥ 404 pg/mL	75.9%	61.4%	1.97	0.39	39.9%	88.3%	65.1%	0.69	4.02	*0.000*	(2.43, 6.65)	0.65	(0.60,0.70)
Total tau ≥ 434 pg/mL*	72.3%	67.1%	2.19	0.41	42.6%	87.8%	68.4%	0.70	4.26	*0.000*	(2.63, 6.89)	0.67	(0.62,0.72)
P-tau 181, per 100 pg/mL									2.05	*0.000*	(1.54, 2.73)	0.69	(0.63,0.75)
p-tau 181 ≥ 56 pg/mL	80.7%	58.7%	1.95	0.33	39.6%	90.1%	64.2%	0.69	5.01	*0.000*	(2.90, 8.65)	0.67	(0.63,0.72)
p-tau 181 ≥ 62.3 mg/mL*	78.3%	65.2%	2.25	0.33	43.1%	89.9%	68.5%	0.72	5.46	*0.000*	(3.23, 9.21)	0.69	(0.64,0.74)
Aβ42/ Aβ40 ratio, per 1 SD									0.54	*0.000*	(0.41, 0.70)	0.64	(0.59,0.70)
Aβ42/ Aβ40 ratio ≤ 0.068	79.5%	50.0%	1.59	0.41	34.9%	87.9%	57.5%	0.65	3.35	*0.000*	(1.97, 5.72)	0.63	(0.58,0.67)
Aβ42/ Aβ40 ratio ≤ 0.054*	65.1%	64.3%	1.84	0.54	38.3%	84.6%	64.7%	0.65	2.97	*0.000*	(1.89, 4.66)	0.64	(0.58,0.69)
Aβ42/p-tau 181 ratio, per 1 SD									0.38	*0.000*	(0.26, 0.54)	0.71	(0.66,0.76)
Aβ42/p-tau 181 ratio ≤ 11.8	80.7%	55.5%	1.81	0.35	37.9%	89.5%	61.8%	0.68	4.49	*0.000*	(2.60, 7.75)	0.66	(0.62,0.71)
Aβ42/p-tau ratio 181 ≤ 8.9*	77.1%	63.6%	2.12	0.36	41.6%	89.2%	67.0%	0.70	4.84	*0.000*	(2.90, 8.08)	0.68	(0.63,0.73)
FDG-PET													
AD like, yes versus no	61.3%	66.2%	1.81	0.59	36.0%	84.6%	65.0%	0.64	2.87	*0.000*	(1.83, 4.50)	0.63	(0.58,0.69)
MRI hippocampal volume, mm^3													
FS right, per 1 SD									0.53	*0.000*	(0.42, 0.68)	0.66	(0.60,0.71)
FS right < 5°p	36.5%	78.2%	1.67	0.82	35.2%	79.1%	67.9%	0.57	2.13	*0.001*	(1.37, 3.32)	0.58	(0.53,0.63)

(Continues)

TABLE 2 (Continued)

	SE	SP	LR+	LR−	PPV	NPV	Accuracy	AUC	HR	*p* value	95% CI	C-index	95%CI
FS right ≤ 3067.027*	63.5%	63.6%	1.74	0.57	36.2%	84.3%	63.6%	0.64	2.85	*0.000*	(1.83, 4.43)	0.63	(0.58,0.68)
FS left, per 1 SD									0.53	*0.000*	(0.42, 0.67)	0.66	(0.60,0.73)
FS left < 5°p	44.1%	79.7%	2.17	0.70	41.1%	81.6%	71.9%	0.62	3.20	*0.000*	(2.07, 4.94)	0.63	(0.57,0.68)
FS left ≤ 2857.771*	54.8%	72.8%	2.01	0.62	39.3%	83.3%	64.8%	0.64	3.10	*0.000*	(2.01, 4.77)	0.64	(0.59,0.69)
AA right, per 1 SD									0.65	*0.000*	(0.53, 0.80)	0.63	(0.57,0.69)
AA right < 5°p	36.5%	81.9%	2.02	0.78	39.7%	79.8%	70.7%	0.59	2.41	*0.000*	(1.55, 3.76)	0.59	(0.54,0.64)
AA right ≤ 4811.911*	68.2%	55.8%	1.55	0.57	33.5%	84.3%	58.8%	0.62	2.43	*0.000*	(1.54, 3.84)	0.60	(0.55,0.65)
AA left, per 1 SD									0.59	*0.000*	(0.48, 0.73)	0.65	(0.59,0.71)
AA left < 5°p	44.7%	79.1%	2.14	0.70	41.3%	81.3%	70.6%	0.62	2.58	*0.000*	(1.68, 3.96)	0.61	(0.55,0.66)
AA left ≤ 4542.296*	67.1%	59.7%	1.66	0.55	35.4%	84.6%	61.5%	0.63	2.67	*0.000*	(1.70, 4.20)	0.62	(0.57,0.67)
EEG													
Delta, per 1 SD									0.89	0.127	(0.76, 1.03)	0.55	(0.49,0.62)
Delta ≤ 1.0007343*	53.6%	60.8%	1.37	0.76	30.4%	80.4%	59.1%	0.57	1.56	*0.043*	(1.01, 2.39)	0.55	(0.50,0.61)
Theta, per 1 SD									0.69	*0.000*	(0.58, 0.82)	0.61	(0.55,0.68)
Theta ≤ 1.0060424*	61.9%	59.3%	1.52	0.64	32.7%	83.0%	59.9%	0.61	2.10	*0.001*	(1.35, 3.27)	0.59	(0.54,0.65)
Alpha1, per 1 SD									1.05	0.587	(0.87, 1.28)	0.54	(0.47,0.60)
Alpha1 ≥ 0.99609017*	47.1%	58.3%	1.13	0.91	26.5%	77.5%	55.6%	0.53	1.23	0.332	(0.81, 1.89)	0.53	(0.48,0.59)
Alpha2, per 1 SD									1.22	*0.030*	(1.02, 1.47)	0.57	(0.50,0.63)
Alpha2 ≥ 1.0007917*	50.6%	70.3%	1.70	0.70	35.3%	81.7%	65.5%	0.60	1.96	*0.002*	(1.28, 3.00)	0.57	(0.52,0.63)
Beta1, per 1 SD									1.10	0.237	(0.94, 1.3)	0.54	(0.47,0.60)
Beta1 ≥ 1.0085127*	61.2%	47.4%	1.16	0.82	27.1%	79.3%	50.7%	0.54	1.39	0.143	(0.90, 2.14)	0.54	(0.49,0.59)
Beta2, per 1 SD									1.01	0.943	(0.86, 1.17)	0.51	(0.45,0.57)
Beta2 ≥ 1.0157197*	47.1%	52.6%	0.99	1.01	24.1%	75.7%	51.3%	0.50	1.05	0.808	(0.69, 1.61)	0.52	(0.46,0.57)
Gamma, per 1 SD									0.93	0.544	(0.75, 1.17)	0.53	(0.46,0.59)
Gamma ≤ 1.0028913*	46.3%	64.3%	1.30	0.83	29.3%	79.0%	59.9%	0.55	1.39	0.130	(0.91, 2.14)	0.54	(0.48,0.59)
SW comb, per 1 SD									1.50	*0.000*	(1.21, 1.86)	0.59	(0.52,0.66)
Predicted class with ML (1 vs 0)	31.0%	70.0%	1.03	0.99	24.8%	76.0%	60.5%	0.50	1.00	0.987	(0.63, 1.58)	0.51	(0.46,0.56)
SWcomb ≥ −0.45*	69.0%	47.1%	1.31	0.66	29.4%	82.7%	52.4%	0.58	1.81	*0.012*	(1.14, 2.88)	0.57	(0.51,0.62)

Note: Italic values refers to significant values.

Abbreviations: AA, ACM AdaBoost; Aβ, amyloid beta; AUC, area under the curve; CSF, cerebrospinal fluid; EEG, electroencephalogram; FCSRT–DFR, Free and Cued Selective Reminding Test – Delayed Free Recall; FDG-PET, fluorodeoxyglucose positron emission tomography; FS, FreeSurfer; HR, hazard ratio (univariate Cox model); LR−, negative likelihood ratio; LR+, positive likelihood ratio; ML, machine learning (1: abnormal, 0: normal); MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value; p-tau181, tau phosphorylated at threonine 181; SD, standard deviation; SE, sensitivity; SP, specificity; SW, small world combination.

*data-driven optimal cut-offs

TABLE 3 Final predictive multivariable Cox model (a) and recalibrated multivariable model (b).

	(a) Final model				(b) Recalibrated model		
	HR	*p*	95% CI		HR	95% CI	
Gender, female versus male	1.90	*0.007*	1.19	3.05	1.66	1.15	2.41
Age, per year	1.06	*0.009*	1.02	1.11	1.05	1.01	1.08
Amsterdam IADL per unit	1.03	*<0.001*	1.02	1.05	1.02	1.01	1.04
Family history, yes versus no	1.69	*0.029*	1.05	2.70	1.51	1.04	2.19
MMSE, per unit	0.84	*0.002*	0.75	0.94	0.87	0.80	0.95
Left hippocampal volume (FS), per 1 SD	0.69	*0.002*	0.54	0.87	0.74	0.61	0.90
Aβ42/p-tau 181 ratio, per 1 SD	0.63	*0.013*	0.44	0.91	0.70	0.52	0.93
SWcomb index, per 1 SD	1.50	*<0.001*	1.20	1.89	1.38	1.15	1.65

Note: The individual 3-year risk score can be calculated by applying the following formula:
[1 − 0.1390(exp[B])] × 100%, where $B = 0.5084 \times$ sex (0 if M, 1 if F) + 0.0461 × age (years) + 0.0246 × Amsterdam IADL score + 0.4142 × family history (0 if no, 1 if yes) − 0.1373 × MMSE corrected − 0.3605 × (Aβ42/p-tau181 ratio)/14 − 0.2964 × Left hippocampal volume (FS)/444 + 0.3215 × SW combined EEG/20.9. Italic values refers to significant values.
Abbreviations: Aβ, amyloid beta; CI, confidence interval; IADL, instrumental activities of daily living; FS, FreeSurfer; MMSE, Mini-Mental State Examination; SD, standard deviation; SWcomb, small world combination.

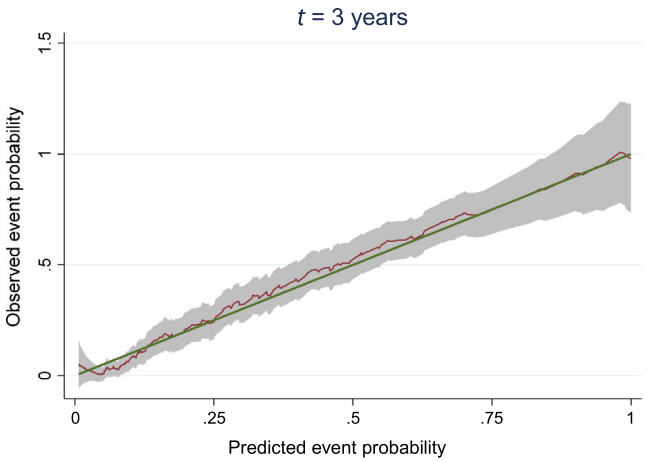

FIGURE 3 Model calibration, observed event probability plotted against predicted event probabilities at 3 years (smoothed line) with pointwise 95% confidence interval. Solid line: line of identity, denoting perfect calibration.

sures may be considered competing predictors. These findings support the decisions made in refining the model, namely, the removal of the Aβ42/Aβ40 ratio and the replacement of right with left hippocampal volume. The model obtained by combining estimates across imputations using Rubin's rules did not substantially differ from the model derived from the complete-case analysis (Table S9).

3.3 | Additional analysis on COVID-19

The comparison of baseline characteristics between participants enrolled before and after the onset of the pandemic is presented in Table S10, showing no evidence of selection bias. Furthermore, the enrollment period was not associated with the hazard of conversion to AD (hazard ratio [HR]: 1.07, 95% CI: 0.85 to 1.36). During the follow-up, 49 COVID-19 infections were recorded in 41 subjects. Of these, five individuals required hospitalization, and one of them needed intensive care. When included as a time-dependent covariate in the Cox model, COVID-19 infection was associated with a non-significant reduction in the risk of conversion to AD (HR: 0.65, 95% CI: 0.20 to 2.15). Caution is warranted in interpreting this result, as 86 participants had missing information regarding COVID-19 infection status, and these individuals showed a higher risk of conversion compared to those who did not contract the infection during the study period (HR: 1.88, 95% CI: 1.09 to 3.24).

4 | DISCUSSION

This multicenter study combined biological, neuroimaging, neurophysiological, sociodemographic, clinical, and neuropsychological data in a MCI cohort followed over 36 months. Harmonization of procedures and centralized biomarker evaluation in expert centers were implemented to minimize inter-center and inter-rater variability, with all biomarker risk assessments conducted blinded to outcomes.[8,9] Both MCI diagnosis and dementia conversion were validated by expert clinicians blinded to biomarker results. The statistical plan was prespecified[8] and planned according with TRIPOD guidelines.[36]

In defining the analysis plan, we prioritized conventional, well-established statistical approaches to develop a prediction tool that is interpretable and readily applicable in clinical practice. This choice is supported by evidence showing that, in dementia risk prediction among individuals with MCI, Cox regression models achieve predictive performance comparable to, and in some cases superior to, more complex machine-learning methods.[50] Moreover, Sánchez-Pinto et al.[51] showed that in small datasets with fewer than 20 events per variable, traditional variable-selection strategies, such as stepwise selection, may offer greater parsimony and stability. The use of multiple impu-

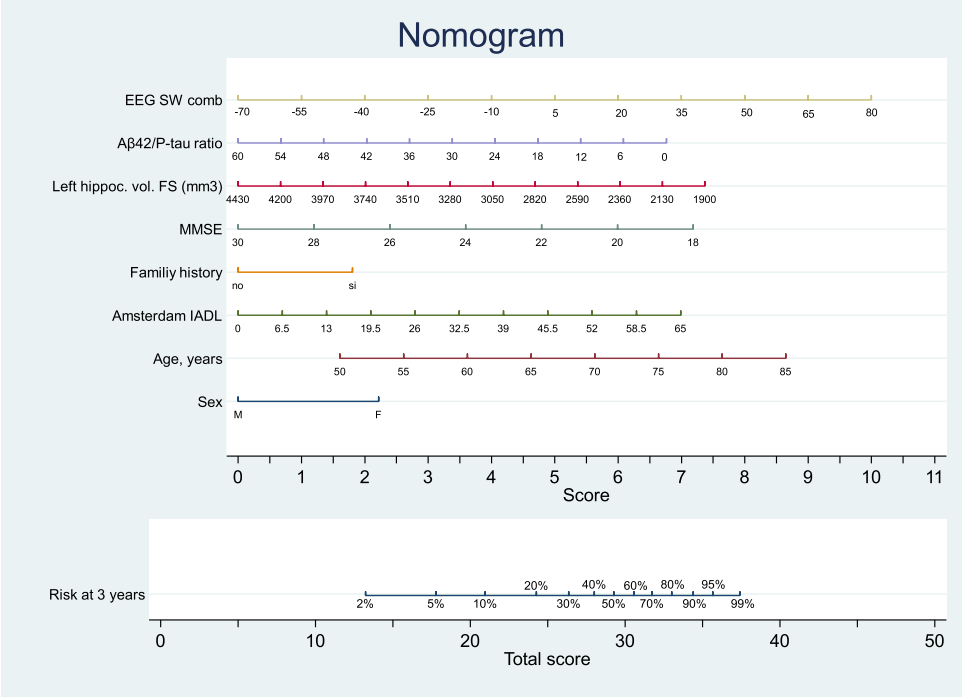

FIGURE 4 Nomogram of recalibrated prediction model. The total score, calculated as the sum of the individual scores, represents the predicted 3-year probability of conversion to Alzheimer's disease (AD). Note on using the nomogram: For each predictor, locate the patient's value on the corresponding axis and draw a vertical line downward to the score axis to determine the assigned score. Repeat this procedure for all predictors. Sum the points obtained for each variable to calculate the total score. Finally, locate it on the total score axis and draw a vertical line downward to estimate the patient's risk of conversion to AD.

tation, competing-risk analysis, and sensitivity analyses addressing the variable-selection process further supported the robustness of our findings and minimized potential methodological bias.

The principal limitation of this study is the limited number of events per predictor. Under such conditions, data-driven variable selection increases the risk of overfitting; therefore, we applied internal validation procedures and model recalibration. Nevertheless, external validation remains essential to confirm generalizability and clinical applicability, and a dedicated validation study is currently planned.

To assess concordance between clinical and biological diagnoses within our cohort, MCI clinical diagnoses were revised under blinded conditions with respect to biomarker data, according to biomarker-informed MCI criteria.[7] Most participants fulfilling MCI clinical core criteria (72.3%) showed a biomarker profile consistent with high–intermediate probability of MCI due to AD. However, only 70 individuals (27.5%) progressed to AD dementia within 3 years. Notably, 15 participants with MCI clinical core criteria and low probability of MCI due to AD nonetheless converted to AD dementia.

Evidence from large multicohort and prospective studies indicates that, although abnormal AD biomarkers increase progression risk, a substantial proportion of biomarker-positive MCI individuals remain clinically stable over 2 to 3 years. In the largest analysis to date, Vos et al.[52] reported 3-year conversion rates of 50% to 61% across biomarker-defined groups, indicating that 39% to 50% did not progress. Similar findings have been reported across PET-, CSF-, and multimodal-based studies.[53–56] Consistent with this literature, our recent analysis in the INTERCEPTOR cohort showed that approximately 60% of amyloid-positive MCI participants remained dementia-free over 3 years.[57] Overall, these findings confirm that even among biomarker-positive MCI individuals, 40% to 50% typically remain clinically stable over a 2- to 3-year period.

Within the rigorous frame of our study design, the reported findings prompt several considerations. (1) The 3-year follow-up demonstrated a rising conversion rate peaking during the second year, followed by a sharp decline in the third year. In a recent systematic review, Salemme et al.[5] observed that the ACR (i.e., the incidence density of all-cause dementia) was lower in studies with longer follow-up (13.1% with a 3-year-follow-up, 11.5% with 3.1 to 5 years, and 7.8% with more than 5 years). We cannot exclude a number of cases with "late conversion" (i.e., >3 years' follow-up); meanwhile, we are confident that with 3-year follow-up duration we targeted the majority of high-risk subjects for risk stratification and remained within a time frame that is most often employed for public health programs. (2) Sociodemographic and clinical data alone showed a discriminative ability of 72% for MCI-to-clinical AD dementia progression. (3) None of the explored instrumental biomarkers, despite harmonized acquisition procedures and centralized evaluation at expert centers, reached a positive predictive value >50% for the 3-year follow-up (we cannot exclude a better performance when including late → 3-year converters). (4) A predictive model combining biomarkers with sociodemographic/clinical

data reached a discrimination ability of 82% and a PPV of 64%. (5) This type of nomogram, either in its simpler form or enriched by selected biomarkers, might be used to stratify the risk of conversion of MCI to dementia (and to clinical AD dementia when required) into high-, medium-, low-risk groups, supporting public-health applications, including screening campaigns for preventive strategies and innovative treatments.

In recent years, several studies have developed prognostic models for MCI-to-dementia conversion.[58,59] However, most studies were conducted on the ADNI cohort in a research setting, which limits generalizability and relies on retrospective collection of the data. Additionally, there is a substantial heterogeneity in biomarker collection and data handling. Compared to previous prognostic models that include nomograms,[60–65] this study is distinctive in investigating several key biomarker modalities – CSF, ApoE, EEG, MRI, FDG-PET and neuropsychological data – in a single, harmonized clinical setting. While the current results are promising, external validation is ongoing to assess generalizability to broader populations. The INTERCEPTOR project approach, as previously clarified in the comparative analysis with other projects, is intended not for clinical trial use but for routine, everyday clinical use, even with paper and pencil in the absence of a digital device. The basic nomogram is free of any additional cost because it includes only the clinical, sociodemographic, and neuropsychological data routinely collected in a dementia center. The potential use of biomarkers in current clinical practice, as widely suggested based on the available evidence,[66,67] depends on the fact that individual biomarkers, carefully evaluated with the statistical approach reported in our article, can improve a nomogram's overall predictive accuracy.

Although a detailed cost-effectiveness analysis was not performed, some considerations are worth noting: FDG-PET is the costliest and least accessible, MRI and CSF are moderately invasive and expensive, and EEG and neuropsychological testing are low-cost and broadly available. The aim of the nomogram is to flexibly integrate clinical, cognitive, and biomarker features, enabling individualized risk assessment even when only specific biomarkers are available. Notably, a model based solely on clinical variables and the MMSE achieved a C-index of 0.76 (Table S5), compared to a C-index of 0.82 for the full model incorporating MMSE, EEG, MRI, CSF, and clinical data. This highlights the potential for meaningful predictions even with reduced technological burden, which is particularly relevant in resource-limited settings at the start of the patient risk evaluation journey.

This study is not a monocentric or industry-sponsored clinical trial, but rather a public health–oriented initiative, launched in 2018 and funded by institutional public health authorities. Its primary aim was to evaluate, in real-world settings, the added value of available biomarkers – particularly those most promising and accessible at that time – in improving the prediction of progression from MCI to overt dementia, with a special focus on clinically defined AD dementia[33].

Importantly, our goal was not to demonstrate the superiority of any single biomarker but to explore how multimodal information could enhance risk stratification in clinically defined MCI patients under real-world conditions. As a byproduct of the main project, blood samples from the INTERCEPTOR cohort were examined to enable a direct comparison between plasma and CSF biomarkers, and results have been reported elsewhere.[22] Plasma Aβ42, the Aβ42/Aβ40 ratio, and p-tau181 showed statistically significant correlations with their CSF counterparts. Moreover, among plasma biomarkers, the Aβ42/Aβ40 ratio and p-tau217 demonstrated robust discriminative performance in distinguishing CSF Aβ+ from Aβ− and Aβ+/ p-tau+ from Aβ−/p-tau− MCI subjects, supporting their diagnostic value for AD pathology.[22] Building on these results, incorporating plasma p-tau and Aβ biomarkers into future predictive models could further enhance early detection accuracy, while offering a minimally invasive, scalable, and cost-effective strategy suitable for broader population.

The study is distinguished by several unique features: (1) a multicenter design involving a coordinated hub-and-spoke model and harmonized clinical, neuropsychological, biological, and imaging protocols; (2) independent risk assessment by expert clinicians blinded to follow-up outcomes; and (3) a focus on translational relevance for early intervention strategies, including pharmacological and non-pharmacological treatments.

While we acknowledge that newer biomarkers, such as plasma p-tau217 or tau PET, have emerged since the study's launch, we believe that our findings provide valuable and complementary insights, particularly for the implementation of predictive tools in public healthcare systems, where access to such advanced technologies may still be limited.

It is of utmost importance to recognize that a consistent percentage of MCI subjects, despite having several altered biomarkers, did not develop dementia during the 3-year follow-up time window.[57,68] A further percentage might progress to overall dementia later, but it is important to consider that in the vast majority of epidemiological studies, the progression rate does not exceed a cumulative threshold of 50%, even with a follow-up duration longer than 3 years. The reasons for non-progressing MCI might be identified in individual brain resilience mechanisms. The identification of protective factors represents the focus of future research, including the development of innovative therapeutic and rehabilitative approaches. Finally, cost analysis provides an opportunity to identify sustainable strategies for the appropriate risk evaluation in the growing MCI population. The ability to identify, at an early stage, MCI subjects at the highest risk of progression and to intervene effectively may represent a key strategy for advancements in this area.

AUTHOR CONTRIBUTIONS

Flavia L. Lombardo: conceptualization, writing, original draft preparation, data analysis, reviewing, and editing. Naike Caraglia: conceptualization, writing, original draft preparation, reviewing, and editing. Patrizia Lorenzini: writing, original draft preparation, and data analysis. Nicola Vanacore, Stefano F. Cappa, Maria Cotelli, Francesco Iodice, Camillo Marra, Francesca Miraglia, Chiara Pappalettera, Daniela Perani, Davide Quaranta, Alberto Redolfi, Patrizia Spadin, Fabrizio Tagliavini, and Fabrizio Vecchio: writing, reviewing, and editing. Paolo M. Rossini: original idea, conceptualization, writing, original draft preparation, reviewing, and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. All author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

Data can be requested from the corresponding author, Paolo M. Rossini (paolomaria.rossini@sanraffaele.it).

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CONSENT STATEMENT

Written informed consent was obtained for all participants before providing data to the Interceptor Project. The study was registered at ClinicalTrials.gov (Identifier: NCT03834402; registration date: February 8, 2019). Ethical approval was granted by the A. Gemelli University Polyclinic Foundation Ethics Committee (Protocol 37756/18 ID: 2251; 27/09/2018).

The study was conducted following the Declaration of Helsinki for the protection of human participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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