REVIEW ARTICLE

Blood biomarkers in MCI conversion to Alzheimer's disease: a systematic review and meta-analysis

Article history:
Received: 03-02-2023
Revised: 19-05-2023
Accepted: 03-06-2023

[a] Department of Neurology and Institute of Neurology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine; Shanghai 200025, China.
[b] Department of Neurology and Institute of Neurology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine; Shanghai 200025, China.
[c] Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China. Institute of Psychology and Behavioral Science, Shanghai Jiao Tong University, Shanghai 200030, PR China.
[d] Department of Neurology and Institute of Neurology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine; Shanghai 200025, China.
[e] Department of Neurology and Institute of Neurology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine; Shanghai 200025, China.
[f] Department of Neurology and Institute of Neurology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine; Shanghai 200025, China.
[g] Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China. Institute of Psychology and Behavioral Science, Shanghai Jiao Tong University, Shanghai 200030, PR China.
Corresponding Author: licb@smhc.org.cn
[h] Department of Neurology and Institute of Neurology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine; Shanghai 200025, China.
Corresponding Author: wg11424@rjh.com.cn
* Contributed equally to the article.

Hai-Xia Li[a,*], Jin-Tao Wang[b,*], Yu Dong[c], Jian-Ping Li[d], Jin-Wen Xiao[e], Ru-Jing Ren[f], Chun-Bo Li[g], Gang Wang[h]

ABSTRACT

Background: The predictive effects of blood biomarkers (BBMs) in the progression of Alzheimer's disease (AD) have been reported recently. However, controversies still exist. In the present study, we aim to identify the predictive performances of BBMs in the conversion from Mild cognitive impairment (MCI) to AD.

Methods: PubMed, Embase, Cochrane Library, and Web of Science from inception to June 10, 2023 were searched. Predictive potentials were evaluated by pooling the ratio of means (ROMs), relative risks (RRs), and diagnostic indexes from MCI-converters (MCI-c: MCI patients who convert to AD) and MCI-non converters (MCI-nc) based on fixed-effects or random-effects. Newcastle–Ottawa Quality Assessment Scale (NOS) was applied for quality assessment.

Results: A total of 44 studies with 9343 participants from 28 cohorts were included in the meta-analysis, whereas the other 45 articles were included in the qualitative review. The average score of 44 studies included in the meta-analysis was 7.125. In pooled ROMs, plasma Aβ42/Aβ40 was lower, whereas Aβ40, T-tau, P-tau 181, P-tau 217, NFL, and GFAP were higher in MCI-c than MCI-nc. In pooled RRs, P-tau (RR=2.50, 95%CI: 2.04-3.06) as a continuous variable, Aβ42/Aβ40 as a categorical variable (RR=1.28, 95%CI: 1.01-1.61) could predict future conversion risk of MCI patients. In diagnostic indexes, the diagnostic odds ratio (DOR) was 42 for P-tau 217 (sensitivity: 91%; specificity: 81%), 15 for P-tau 181 (sensitivity: 81%; specificity: 78%), 12.71 for GFAP (sensitivity: 71%; specificity: 86%), 6 for Aβ42/Aβ40 (sensitivity: 86%; specificity: 49%, and 6 for NFL (sensitivity: 80%; specificity: 61%).

Conclusion: Here, our results indicated that blood biomarkers held promising potential in predicting MCI conversion. However, more prospective cohorts based on particular MCI types and high-sensitivity assays are warranted to validate the results next.

KEYWORDS: blood biomarkers; mild cognitive impairment; Alzheimer's disease.

1. INTRODUCTION

As the most common type of dementia worldwide, Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive decline and progressive memory loss. With the advancing aging of the global population, about 1 in 9 people over age 65 have AD,

two-thirds of which are women. Mortality due to AD between 2000 and 2019 has more than doubled, increasing by 145%, resulting in an enormous disease burden ("2023 Alzheimer's disease facts and figures," 2023; J. T. Wang *et al.*, 2022). Therefore, early identification and intervention play a fundamental role in AD.

The evolution of the diagnostic criteria for AD epitomizes the convergence of clinical observation with advanced biotechnological insights. Before 1984, the standardized criteria for AD diagnoses were inconsistent. The introduction of the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) in 1984 marked a propounding shift, delineating "possible," "probable," and "definite" AD diagnostic categories (G. McKhann *et al.*, 1984). After 2000, advancements in neuroimaging and CSF analyses highlighted biomarkers like amyloid plaques and tau tangles, enhancing diagnostic precision. The 2011 NIA-AA criteria integrated these biomarkers, underscoring "preclinical AD" stages (G. M. McKhann *et al.*, 2011). The 2018 NIA-AA revision pioneered the AT(N) framework that consisted of Aβ deposition, tau pathology, and neurodegeneration (Jack *et al.*, 2018). More recently, the introduction and renovation of biomarkers of ATNIVS frame in 2023 NIA-AA (A: Aβ proteinopathy; T: AD tau proteinopathy; N: injury, dysfunction, or degeneration of neuropil; I: inflammation, astrocytic activation; V: vascular brain injury; S: α-synuclein) incorporated blood biomarkers for AD diagnosis and staging. This underpinned current AD diagnosis, promoting accurate detection and refining research avenues.

Generally speaking, the AD continuum comprises preclinical AD, mild cognitive impairment (MCI) due to AD, and AD dementia. Of note, heterogeneous MCI can be divided into 2 clinical phenotypes, amnestic MCI (aMCI) and non-amnestic MCI (naMCI) (Petersen, 2004), based on the presence of memory impairment. aMCI is regarded as prodromal AD, while naMCI tends to develop non-AD dementia. When incorporating biomarkers, MCI can also be diagnosed as MCI due to AD with positive pathophysiological biomarkers (Albert *et al.*, 2011). Among MCI patients, around 15% develop dementia after two years; one-third progress to AD dementia within five years. However, 26% MCI patients will reverse cognitive normal. Hence, finding reliable biomarkers and identifying MCI subjects prone to develop dementia is a crucial task of current research ("2023 Alzheimer's disease facts and figures," 2023).

However, to some extent, expensive PET imaging and invasive lumber puncture have restricted the application of imaging CSF examinations. Here, blood-based biomarkers (BBM) might be a resourceful tool for appraising AD risk and tailoring interventions with their cost-effective, less invasive, and serially-measured nature. First and foremost, plasma Aβ and P-tau are associated with corresponding levels in CSF, with Aβ-PET (Barthélemy, Horie, Sato, & Bateman, 2020) or tau-PET scans (Bilgel *et al.*, 2023), and post-mortem AD pathology (Z. B. Wang *et al.*, 2023), differentiating AD dementia from other forms of dementia (Hampel *et al.*, 2021; Hansson *et al.*, 2022; Teunissen *et al.*, 2022). Secondly, in temporal order, plasma P-tau 217 and P-tau 231 can capture the earliest brain amyloid alterations before the overt amyloid plaque is formed. Besides, Aβ42/Aβ40 declines 41 years before Aβ-PET positivity. Thirdly, accumulating evidence has reported the predictive roles of blood biomarkers in AD continuum. Taken together, the aforementioned aspects highlight BBMs as surrogate biomarkers in the progression of AD.

Nevertheless, the predictive effects of candidate BBMs in the conversion from MCI to AD remain undetermined so far. Hence, we conducted a comprehensive meta-analysis focusing mainly on four categories of biomarkers—amyloid, phosphorylated tau (P-tau), neurofilament light (NFL), and glial fibrillary acidic protein (GFAP). Meanwhile, to optimize the generalizability and scalability of the pooled results, we discussed the variances between MCI and aMCI groups given that aMCI patients are more prone to develop AD compared with naMCI and that different diagnostic might bring heterogeneity of these results. Besides, we also deliberate on discrepancies among different measuring methods. In the end, we also summarized other novel and emerging biomarkers in the qualitative review.

2. MATERIALS AND METHODS

This meta-analysis was registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/) with a CRD of 42023404506 and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (McInnes *et al.*, 2018) **(Supplementary material 1).**

2.1. Search strategy

PubMed, Web of Science, Cochrane Library, and Embase from inception to June 10, 2023 were independently searched by two study investigators (HL and JW). The following three parts of search strings were applied and combined with Boolean Operator "AND" **(Supplementary material 2).** The first section referred to AD and MCI. The second referred to blood biomarkers, and the third to study types. To avoid omission, we manually scrutinized the references of key retrieved articles and relevant reviews.

2.2. Selection criteria

Articles were included if they satisfied the following four conditions: (1) articles from peer-reviewed journals and investigating human participants; (2) the diagnosis of MCI and AD are in agreement with recognized diagnostic criteria. (3) reporting at least one AD blood-based biomarker at baseline. (4) for longitudinal investigations, the clinical diagnosis of the participants should be reported in the follow-up duration. The exclusion criteria are demonstrated in **Figure 1.** To avoid double-counting participants by including more than one publication from the same cohort, we only selected one of the publications that reported the largest number of cases or had the longest follow-up duration. The literature selection was performed by two experienced investigators (HL and WJ). Discrepancies were resolved by consensus with a third neurologist (GW).

2.3. Data extraction and quality assessment

Two reviewers (HL and WJ) independently implemented data extraction and quality appraisal of included studies. Discrepancies were resolved by discussing with a third neurologist (GW). The following information was extracted: (1) basic information — the name of the first author, publication year, study cohort, region, study type, follow-up duration, sample type, assay methods; (2) subjects' information-MCI criteria, AD criteria gender, MCI type, the number of MCI converters and non-converters, APOE carriers, education years, baseline age and MMSE; (3) blood biomarker's information-baseline concentrations of blood biomarkers, effect sizes and 95% CIs, true-positive (TP), false-positive (FP), true-negative (TN), and false-negative (FN) values. The authors were contacted for essential information. The NOS scale was exploited for quality assessment (Stang, 2010). Studies scoring 7–9 are of high quality, 4–6 of moderate quality, and less than 4 of low quality.

2.4. Statistical analysis

Blood biomarkers reported in no less than four studies were pooled in meta-analysis. The primary outcome was the clinical conversion from MCI to AD, further denoted by ratios of means (ROM), relative risks (RR), and diagnostic indicators. ROM method was used to calculate the ratio of biomarker concentrations between MCI-c and MCI-nc. A ratio above one indicates that the level of BBM is higher in MCI-c than that of MCI-nc (Friedrich, Adhikari, & Beyene, 2008; Olsson *et al.*, 2016). Heterogeneity was examined by Q test and I^2 statistic. I^2 values >50% or $p<0.1$ of Q test represented significant heterogeneity. A fixed-effects model was applied when $p>0.1$ and I^2 <50%; otherwise, a random-effects model was used. To investigate the sources of heterogeneity and respective pooled effects among different groups, subgroup analyses were conducted based on MCI type, methods, region, study type, follow-up duration, baseline age, female percent, APOE *ε4* status, and MMSE. Meta-regression analyses were also applied. Sensitivity analyses were employed by a leave-one-out strategy to detect the stability of the pooled results. Publication bias was assessed by Egger's tests and visualized by the funnel plots. "Trim and fill" strategy was used to assess whether pooled results were affected by publication bias. For diagnostic indexes, the pooled sensitivity, specificity, PLR, NLR, and DOR were computed with TP, FP, TN, and FN. HSROC curve was adopted to evaluate the correlation between sensitivity and specificity. Deek's funnel plot asymmetry test was employed to test publication bias. All statistical analyses were performed using STATA version 15. P-values less than 0.05 were considered significant. Biomarkers that were reported in less than 4 studies were mainly discussed in the qualitative review.

3. RESULTS

3.1. Characteristics of included studies and quality appraisal

After retrieving 6718 studies, there were 89 eligible studies **(Supplementary material 3).** Forty-four

studies containing 10 biomarkers were included in meta-analyses, while the other 45 articles were included in systematic review due to the insufficient number of studies (<4) **(Figure 1).** In all, 44 studies enrolled a total of 9343 participants from 28 cohorts with sample sizes ranging from 33 to 584 subjects. The characteristics of the included studies are listed in **Table 1.** Twenty-eight studies reported baseline concentrations of blood biomarkers **(Supplementary material 4);** Twenty-two studies measured effect sizes and 95%Cis **(Supplementary material 4);** Twelve studies reported diagnostic indexes **(Supplementary material 4).** Overall, 10 blood biomarkers (Aβ42, Aβ40, Aβ42/ Aβ40, T-tau, P-tau 181, P-tau 217, NFL, GFAP, BDNF, and APOE) were identified. The average NOS score of the included studies was 7.125, all of which were rated as having moderate to high quality **(Supplemental material 5).**

3.2. Results of meta-analysis

3.2.1. ROMs of blood biomarkers

Aβ42, Aβ40, Aβ42/Aβ40, T-tau, P-tau 181, P-tau 217, NFL, GFAP, and BDNF were analyzed by ROM method in 28 articles **(Figure 2, Supplementary Fig. 1-9).** Plasma Aβ42/Aβ40 (0.93, 95%CI: 0.89-0.97), BDNF (0.97, 95%CI: 0.95-0.99) were lower in MCI converters (MCI-c) than MCI nonconverters (MCI-nc). Aβ40 (1.04, 95%CI: 1.02-1.07), T-tau (1.19, 95%CI: 1.11-1.28), P-tau 181 (1.43, 95%CI: 1.31-1.55), P-tau 217 (1.86, 95%CI: 1.53-2.27), NFL (1.23, 95%CI: 1.09-1.39), GFAP (1.65, 95%CI: 1.50-1.81) were higher in MCI-c than MCI-nc. However, the pooled result became unstable after removing Xie 2017 for BDNF (0.95, 95%CI: 0.86-1.05). No differences were found for Aβ42 (1.01, 95%CI: 0.95-1.08) between MCI-c and MCI-nc.

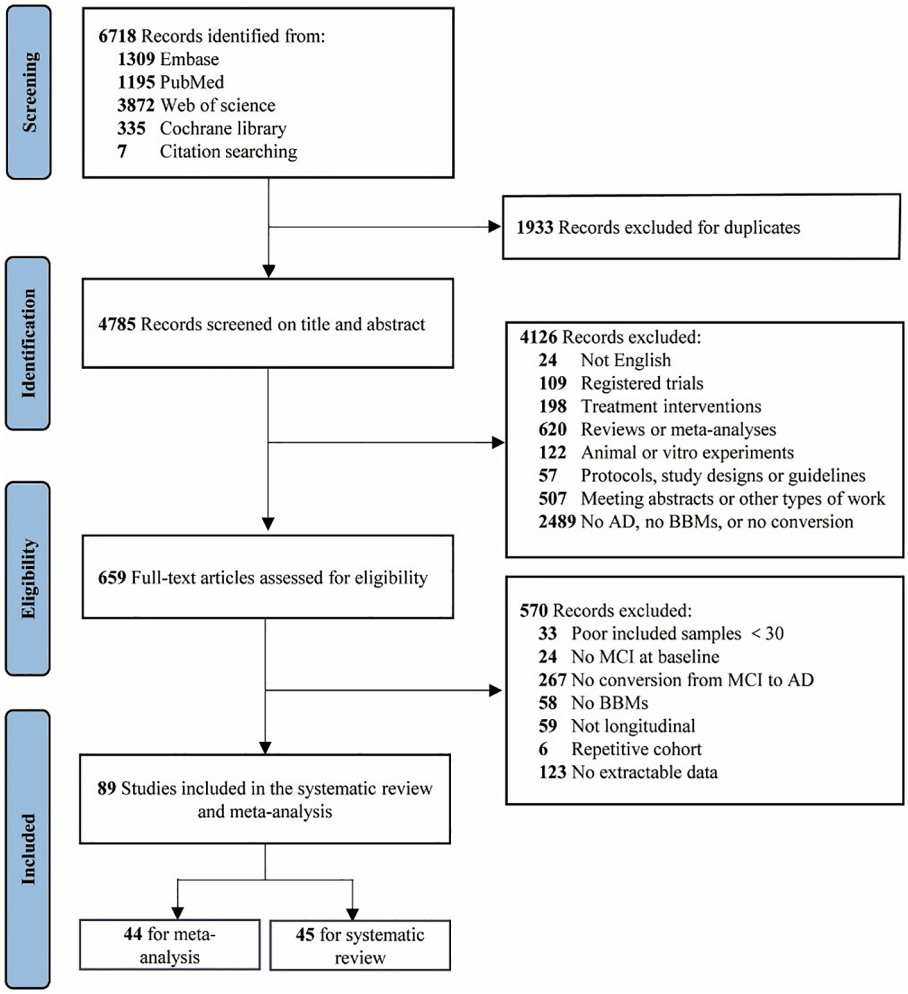

Figure 1. The flow chart of literature selection.

Study	Sample Resource	Region	Sample Types	MCI Criteria	AD Criteria	Follow-up Duration mean/median (y)	Sample Type	Assay Method (Detection instruments /Antibodies)	MCI Type	MCI Cases		Female	Age Mean (SD)/ Median (IQR)	APOE4 Carriers (%)	MMSE Mean (SD)/ Meidan (IQR)	Education Years Mean (SD)	Blood Biomarkers	SON
										MCI-nc	MCI-c							
2008 Blasco	Vienna Transdanube Aging (VITA)	Europe	Community	Petersen 2001 IWG 2004	NINCDS-ADRDA	mean 2.5y	Plasma	ELISA Innogenetics	MCI	40	41	NA	NA	NA	NA	NA	Aβ42 pg/ml	7
2008 Lopez	Pittsburgh Cardiovascular Health Study Cognition Study (CHS-CS)	America	Community	CHS cognition study MCI criteria	NINCDS-ADRDA	mean 4.5y	Plasma	ELISA 6E10	MCI	9	33	52.38	79.79 (4.3)	28.57	NA	NA	Cystatin C mg/l Aβ42 pg.ml Aβ40 pg/ml Aβ42/Aβ40	8
2009 Cammarata	NA	Europe	Clinical	Petersen 2001	NINCDS-ADRDA	mean 2y	Plasma	ELISA IBL, Gumna Japan	aMCI	42	37	NA	75.16 (5.16)	NA	NA	NA	Aβ42 pg/ml Aβ40 pg/ml Aβ42/Aβ40 Aβ pg/ml	8
2010 Hansson-A	Malmö University Hospital	Europe	Clinical	Petersen 1999 Petersen 2004	DSM-IIIR NINCDS-ADRDA	mean 5.2y range 4-6.8y	Plasma	xMAP Innogenetics	aMCI	51	48	59.60	69.25 (8.05)	65.60	26.95 (1.67)	NA	Aβ40 ng/L Aβ42 ng/L Aβ42/Aβ40	8
2010 Hansson-B	Göteborg MCI study	Europe	Clinical	NA	NA	mean 2.5y range 1.9-3.9 y	Plasma	xMAP Innogenetics	MCI	88	15	48.54	62.36 (6.56)	45.31	28.77 (1.22)	NA	Aβ40 ng/L Aβ42 ng/L Aβ42/Aβ40	8
2010 Lui	AIBL	Australia	Community	Petersen 1999 IWG 2004	NINCDS-ADRDA	NA	Plasma	xMAP Innogenetics	MCI	122		55.70	75.9 (7.5)	49.60	26.2 (2.6)	NA	Aβ42 pg/ml Aβ40 pg/ml Aβ42/Aβ40	5
2011 Ma	Epidemiology of cognitive Aging (ECA) study	Asia	Community	Petersen 2001	DSM-IIIR criteria NINCDS-ADRDA	mean 5.2 y range 4.0-6.8 y	Plasma	ELISA R162 R165	aMCI	240	245	62.89	70.04 (5.63)	50.52	26.84 (1.69)	6.75 (1.62)	Aβ42 ng/ml Aβ40 ng/ml Aβ42/Aβ40	7
2011 Toledo	ADNI	America	Community	ADNI Criteria	NINCDS-ADRDA	mean 2y	Plasma	xMAP Innogenetics	aMCI	162	145	34.53	74.65 (7.39)	NA	27.14 (1.75)	15.82 (2.91)	Aβ40 pg/ml Aβ42 pg/ml Aβ42/Aβ40	8
2014 Kiddle	EU funded AddNeuroMed (ANM) Alzheimer's Research Trust (ART)	Europe	Clinical Community	NA	NINCDS-ADRDA	mean 1y	Plasma	SOMAscan —	MCI	106	43	61.74	76.71 (9.70)	39.60	26.86 (2.33)	NA	APOE	8
2015 Apostolova	ADNI	America	Community	ADNI Criteria	NINCDS-ADRDA	mean 3y	Plasma	NA	aMCI	137	161	35.23	74.74 (7.32)	33.56	27.11 (2.89)	15.75 (2.9)	BDNF, log10 ng/mL	8
2015 Forlenza	Psychogeriatric Clinic of the Institute of Psychiatry, Faculty of Medicine, University of São Paulo	America	Clinical	Petersen 2001	NINCDS-ADRDA	mean 3.9y SD 0.9y	Serum	ELISA	aMCI	42	14	75.00	72.2 (6.2)	29	26.3 (3)	9.9 (5.7)	BDNF pg/ml	7
2015 Wang	NA	Asia	Clinical	Petersen 2004	DSM-IIIR NINCDS-ADRDA	mean 2y	Serum	ELISA	aMCI	68	64	46.21	71.85 (7.21)	51.52	26.70 (1.76)	NA	BDNF ng/ml	7

Study	Sample Resource	Region	Sample Types	MCI Criteria	AD Criteria	Follow-up Duration mean/median (y)	Sample Type	Assay Method (Detection instruments /Antibodies)	MCI Type	MCI Cases		Female	Age Mean (SD)/ Median (IQR)	APOE4 Carriers (%)	MMSE Mean (SD)/ Meidan (IQR)	Education Years Mean (SD)	Blood Biomarkers	SON
										MCI-nc	MCI-c							
2017 Mielke	Mayo Clinic Study of Aging (MCSA)	America	Community	Petersen 2004	NIA-AA 2011	median 3y range 1.1-4.9y	Plasma	SIMOA —	MCI	103	20	NA	NA	NA	NA	NA	T-tau pg/ml	7
2017 van Harten	Amsterdam Dementia Cohort	Europe	Clinical	Petersen 1999 Petersen 2004 NIA-AA 2011	NINCDS-ADRDA	mean 2.3y SD 1.3y	Plasma	ELISA —	aMCI	132	91	42	67.1 (8.2)	58	26.6 (2.4)	NA	APOE mg/l	7
2017 Xie	Mild cognitive impairment and Alzheimer's disease Study in Hebei province (MASHB)	Asia	Community	Petersen 1999	NINCDS-ADRDA	mean 5.08 y SD 0.32y	Serum	ELISA —	aMCI	330	128	45.34	71.62 (5.06)	NA	24.29 (2.16)	3.38 (1.04)	BDNF ng/mL	7
2018 Westwood	GE067-005 Study	Europe America	Clinical	Petersen 2005	NINCDS-ADRDA	mean 3y	Plasma	Immunoassay —	aMCI	121	52	50.30	NA	NA	NA	NA	Aβ40	7
2019 Lopez	Ginkgo Evaluation of Memory Study (GEMS)	America	Community	Cognitive impair-ments and CDR	DSM-IV	mean 8.5y	Plasma	ELISA —	MCI	182	265	NA	NA	NA	NA	NA	Aβ42 pg/ml Aβ42/Aβ40	7
2019 Pérez-Grijalba	AB255 study	Europe	Clinical	Petersen 2004	DSM-IV	mean 2y	Plasma	ELISA Araclon Biotech Ltd, Spain	aMCI	81	62	51.70	73.87 (5.11)	55.20	NA	9.20 (4.04)	Aβ42/Aβ40	6
2019 Chen	Taipei Veterans General Hospital	Asia	Clinical	NIA-AA 2011	NIA-AA 2011 NINCDS-ADRDA	mean 3y	Plasma	ELISA Immuno-Biological Laboratories Co., Ltd. Japan Invitrogen, Carlsbad, CA, USA Life Technologies Corp., Frederick, MD, USA	aMCI	23	10	36.40	78.55 (2.38)	36.40	26.92 (1.58)	11.47 (2.13)	Aβ42 Aβ40 T-tau P-tau 181 Aβ42/Aβ40 Aβ42/t-tau Aβ42/P-tau	8
2020 Cheng	National Taiwan University Hospital	Asia	Clinical	NIA-AA 2011	NIA-AA 2011	mean 2y	Plasma	IMR —	MCI	69	10	NA	NA	NA	NA	NA	T-tau pg/ml Aβ42 pg/ml Aβ40 pg/ml Aβ42/Aβ40	7
2020 Janelidze	Biofinder	Europe	Clinical	Petersen 2004	DSM-5 $A\beta^{+}$	mean 4.9y SD 1.3y	Plasma	P-tau 181: MSD, Biotinylated-AT270, SULFO-TAG-LRL Aβ42, Aβ40, T-tau: Elecsys	P-tau 181-ROM: MCI due to AD Effect sizes: MCI	29	50 Total number for Effect sizes is 117	43.21	73 (69-76)	NA	27 (26-28)	10 (8-13)	P-tau 181 pg/ml T-tau pg/ml Aβ42/Aβ40	6
2020 Shen	ADNI	America	Community	MMSE score of 24 to 30 CDR-SB score of at least 0.5	NINCDS-ADRDA	mean 8y	Plasma	MS —	aMCI	40	7	48.94	68.94 (6.31)	48.94	28.72 (1.49)	16.38 (2.5)	Aβ42/Aβ40	7

https://doi.org/10.37819/hb.2.1758

Study	Sample Resource	Region	Sample Types	MCI Criteria	AD Criteria	Follow-up Duration mean/median (y)	Sample Type	Assay Method (Detection instruments /Antibodies)	MCI Type	MCI Cases		Female	Age Mean (SD)/ Median (IQR)	APOE4 Carriers (%)	MMSE Mean (SD)/ Meidan (IQR)	Education Years Mean (SD)	Blood Biomarkers	SON
										MCI-nc	MCI-c							
2020 Sugarman	BU ADC Clinical Core Registry	America	Community	IWG 2004	NINCDS-ADRDA	mean 5.10y SD 2.78y	Plasma	SIMOA —	MCI due to AD	33	24	NA	NA	NA	NA	NA	NFL pg/ml T-tau pg/ml	6
2020 Westwood	EMIF-ADMBD-Oxford	Europe	Clinical	Petersen 2004 IWG 2004	NINCDS-ADRDA	mean 2.21y	Plasma	xMAP —	MCI	400		NA	NA	NA	NA	NA	APOE	6
2021 Blazhenets	ADNI	America	Community	ADNI Criteria	NINCDS ADRDA	median 4y IQR 4-4.25y	Plasma	SIMOA —	aMCI	80	56	41.91	72.4 (0.7)	71.00	27.6 (1.9)	NA	NFL pg/ml	6
2021 Cicognola	Memory Clinic at Skåne University Hospital, Malmö	Europe	Clinical	Petersen 1999	DSM-IIIR NINCDS-ADRDA Aβ+	mean 4.7y	Plasma	SIMOA —	aMCI	79	47	61.29	71.61 (8.03)	57.06	NA	NA	GFAP pg/ml	7
2021 Cullen-Biofinder	Biofinder	Europe	Clinical	Petersen 2004	DSM-IV	mean 4y	Plasma	Aβ42/Aβ40: Elecsys Aβ42/Aβ40: MS (Araclon Biotech) P-tau 181: MSD (Eli Lilly) NFL: SIMOA P-tau 217: MSD (Biotinylatedβl-BA493, SULFOβ-TAG-4G10-E2)	MCI	145		35.50	71.36 (5.47)	NA	27.21 (1.72)	11.18 (3.49)	Aβ42/Aβ40: MS pg/ml P-tau 181 pg/ml NFL pg/ml Aβ42/Aβ40: MS pg/ml P-tau 217 pg/ml	6
2021 Cullen-ADNI	ADNI	America	Community	ADNI Criteria	NINCDS-ADRDA	mean 4y	Plasma	Aβ42/Aβ40: MS P-tau 181: SIMOA (Quanterix) NFL: SIMOA	MCI	145		35.50	71.36 (5.47)	NA	27.21 (1.72)	11.18 (3.49)	Aβ42/Aβ40: MS pg/ml P-tau 181 pg/ml NFL pg/ml Aβ42/Aβ40: MS pg/ml P-tau 217 pg/ml	6
2021 Cullen-ADNI	ADNI	America	Community	ADNI Criteria	NINCDS-ADRDA	mean 4y	Plasma	Aβ42/Aβ40: MS P-tau 181: SIMOA (Quanterix) NFL: SIMOA	aMCI	86		51.20	71.51 (7.59)	NA	28.26 (1.74)	16.43 (2.67)	Aβ42/Aβ40 pg/ml P-tau 181 pg/ml NFL pg/ml	6
2021 Darmanth'e	ADNI	America	Community	ADNI Criteria	NINCDS-ADRDA	mean 4.19y SD 2.33y	Plasma	SIMOA (Quanterix)	aMCI	299	141	41.80	73.48 (7.55)	NA	27.93 (1.77)	16.01 (2.82)	NFL ng/l	7
2021 Karikari	ADNI	America	Community	ADNI Criteria	NINCDS-ADRDA	mean 3.11y	Plasma	SIMOA (Quanterix)	aMCI	446		NA	NA	NA	NA	NA	P-tau 181 pg/ml	7
2021 Palmqvist-Biofinder	Biofinder	Europe	Clinical	Petersen 2004	DSM-IV	mean 4y	Plasma	P-tau 217 MSD (Biotinylated-IBA493, SULFO-TAG-4G10-E2)	MCI	98	58	NA	NA	NA	NA	NA	P-tau 217 pg/ml NFL pg/ml	7
2021 Palmqvist-ADNI	ADNI	America	Community	ADNI Criteria	NINCDS-ADRDA	mean 4y	Plasma	SIMOA	aMCI	223	86	NA	NA	NA	NA	NA	P-tau 181 pg/ml	7

Study	Sample Resource	Region	Sample Types	MCI Criteria	AD Criteria	Follow-up Duration mean/median (y)	Sample Type	Assay Method (Detection instruments /Antibodies)	MCI Type	MCI Cases		Female	Age Mean (SD)/ Median (IQR)	APOE4 Carriers (%)	MMSE Mean (SD)/ Meidan (IQR)	Education Years Mean (SD)	Blood Biomarkers	SON
										MCI-nc	MCI-c							
2021 Shen	ADNI	America	Community	ADNI Criteria	NINCDS-ADRDA	mean 2y	Plasma	SIMOA (Tau12 and AT270)	aMCI	440	77	NA	NA	NA	NA	NA	P-tau 181 pg/ml	7
2021 Simrén	ANM	Europe	Clinical	Petersen 1999	DSM V NINCDS-ADRDA	mean 1y	Plasma	SIMOA	aMCI	88	19	52.20	74.47 (5.89)	36.40	27.21 (1.82)	8.97 (4.28)	P-tau 181 pg/ml NFL pg/ml Aβ42 pg/ml Aβ42/Aβ40 pg/ml T-tau pg/ml GFAP pg/ml	8
2021 Therriault	ADNI	America	Community	ADNI Criteria	NINCDS-ADRDA	median 4.1y SD 1.34y	Plasma	SIMOA (Quanterix)	aMCI	584		NA	NA	NA	NA	NA	P-tau 181 pg/ml	7
2022 Giannisis	University Hospital, Trondheim, Norway	Europe	Clinical	IWG 2004	NINCDS-ADRDA	mean 2y	Plasma	NFL: SIMOA (Quanterix) APOE: NA	aMCI	30	28	52.45	64.01 (5.24)	68.97	27.33 (1.46)	NA	NFL pg/mL [median min-max] APOE ug/ml [median IQR]	8
2022 Hanon	BALTAZAR	Europe	Clinical	Petersen 1999 IWG 2006	NIA-AA 2011	mean 3y	Plasma	xMAP Innogenetics	MCI	340	145	60.40	77.7 (5.5)	39.60	26.4 (2.5)	NA	Aβ40 pg/ml Aβ42 pg/ml Aβ42/Aβ40	7
2022 Kivisakk	Massachusetts Alzheimer's Disease Research Center (MADRC)	America	Clinical	NIA-AA 2011	NIA-AA2011	mean 5y	Plasma	Peoteins: Olink PEA Aβ42, A40: ELISA (Lübeck, Germany) P-tau 181: SIMOA (Quanterix)	MCI due to AD	30	30	50.00	NA	35	NA	NA	Aβ42/40 P-tau 181 NFL	7
2022 Lee	Korean Brain Aging Study for the Early Diagnosis and Prediction of AD (KBASE-V)	Asia	Clinical	NIA-AA 2011	DSM-IV-TR NIA-AA 2011	mean 2.78y SD 0.63y	Plasma	SIMOA (Quanterix)	MCI due to AD	34	19	43.40	73.27 (8.35)	22.64	23.28 (4.14)	9.31 (3.99)	NFL pg/ml	7
2022 Pichet Binette	Multicentter	America Europe	Clinical	Petersen 2005	NINCDS-ADRDA $A\beta^{+}$	mean 3y	Plasma	P-tau 217: MSD (Eli Lilly) NFL, AB42, AB40: SIMOA (Quanterix)	aMCI	84	26	47.27	72.29 (8.26)	35	NA	13.81 (3.96)	P-tau 217 pg/ml NFL pg/ml AB42/AB40	8
2022 Pichet Binette	Multicentter	America Europe	Clinical	Petersen 2005	NINCDS-ADRDA $A\beta+$	mean 3y	Plasma	GFAP: SIMOA (Quanterix)	aMCI	21	59	NA	NA	NA	NA	NA	GFAP, pg/ml	
2022 Xiao	Shanghai Memory Study (SMS)	Asia	Clinical	Petersen 2004	DSM-IV NINCDS-ADRDA	median 4.7y range 0.9-8.1y	Plasma for others Serum for NFL	SIMOA (Quanterix)	aMCI	163	88	49.80	71.6 (8.2)	25.90	27 (25-29)	11.7 (3.8)	Log-Trans-formed Aβ40 pg/ml Aβ42 pg/ml Aβ42/Aβ40 P-tau 181 pg/ml T-tau pg/ml NFL pg/ml	7

https://doi.org/10.37819/hb.2.1758

Study	Sample Resource	Region	Sample Types	MCI Criteria	AD Criteria	Follow-up Duration mean/median (y)	Sample Type	Assay Method (Detection instruments /Anticbodies)	MCI Type	MCI Cases		Female	Age Mean (SD)/ Median (IQR)	APOE4 Carriers (%)	MMSE Mean (SD)/ Meidan (IQR)	Education Years Mean (SD)	Blood Biomarkers	SON
										MCI-nc	MCI-c							
2022 Zhao	NRHAD	Asia	Clinical	Petersen 1999 Petersen 2004	NIA-AA 2011	mean 2.89y	Serum	xMAP	aMCI	67	23	54.44	69.64 (4.3)	36.67	NA	10.58 (3.24)	Aβ42 pg/ml	9
2023 Janelidze	Memory Clinic at Skåne University Hospital in Malmö	Europe	Clinical	Petersen 2004	DSM-IIIR NINCDS-ADRDA Aβ+	mean 4.9y SD 2.1y	Plasma	P-tau 217 MS MSD SIMOA P-tau 181 MS MSD SIMOA Lumipulse P-tau 213 SIMOA	aMCI	90	45	60.70	74 (66-79)	55.60	28 (26-29)	NA	P-tau 217 pg/ml P-tau 181 pg/ml P-tau 231 pg/ml	7
2023 Kivisäkk	Massachusetts Alzheimer's Disease Research Center (MADRC)	America	Clinical	NIA-AA 2011	NIA-AA2011	mean 4y	Plasma	MSD	MCI due to AD	38	47	47.02	76.64 (8.11)	NA	27.09 (3.45)	NA	P-tau 181 pg/mL T-tau pg/mL NFL pg/mL GFAP pg/mL	8
2023 Kwon	KBASE-V	Asia	Clinical	NIA-AA 2011 Petersen 2001	DSM-IV NIA-AA 2011	mean 2.76y SD 0.63y	Plasma	SIMOA (Quanterix)	aMCI	33	16	NA	NA	NA	NA	NA	P-tau 181 pg/ml	7
2023 Lehmann	BALTAZAR	Europe	Clinical	Petersen 2004	DSM IV-TR NINCDS-ADRDA	Range 0.5-3y	Plasma	SIMOA (Quanterix)	MCI	332	144	61.40	77.7 (5.5)	39.80	26.4 (2.5)	NA	P-tau 181 pg/mL	7
2023 Silva-Spínola	Coimbra University Hospital	Europe	Clinical	NIA-AA 2011	NIA-AA 2011	mean 5.8y SD 3.4y	Serum for NFL GFAP Plasma for Aβ42/Aβ40, T-tau, P-tau 181	SIMOA (Quanterix)	MCI due to AD	46	60	61.00	66.94 (9.77)	42	NA	5.76 (3.76)	GFAP pg/mL NFL pg/mL P-tau 181 pg/mL Aβ42/Aβ40 T-tau pg/ml	7

Table 1. Characteristics of included studies.

For variances attributed to MCI types **(Figure 2),** the differences between converters and non-converters were significant only in aMCI rather than MCI for Aβ40 and Aβ42/Aβ40. For P-tau 181, the differences were significant not only in a MCI, but also in MCI due to AD and MCI. For NFL, the differences were significant in aMCI but not MCI due to AD. In terms of measuring methods, ELISA assays tested higher Aβ40 (1.069, 95%CI: 1.03-1.11) and lower Aβ42/Aβ40 (0.902, 95%CI: 0.847-0.96) on MCI-c to MCI-nc. SIMOA assays showed lower Aβ42/Aβ40 (0.928, 95%CI: 0.896-0.961), higher T-tau (1.142, 95%CI: 1.049-1.244), P-tau 181 (1.493, 95%CI: 1.36-1.639), P-tau217 (1.746, 95%CI: 1.234-2.47), NFL (1.283, 95%CI: 1.123-1.465) and GFAP (1.675, 95%=1.505-1.865). IMR showed higher T-tau (1.523, 95%CI: 1.245-1.863). MSD showed higher P-tau 181 (1.574, 95%CI: 1.375-1.803), P-tau217 (1.939, 95%CI: 1.233-3.05) and GFAP (1.108, 95%CI: 0.875-1.404). MS showed higher P-tau 181 (1.162, 95%CI: 1.038-1.3) and P-tau 217 (1.894, 95%CI: 1.477-2.43). As outlined above, the pooled ROMs vary depending MCI types and assays, which should be underscored in future studies.

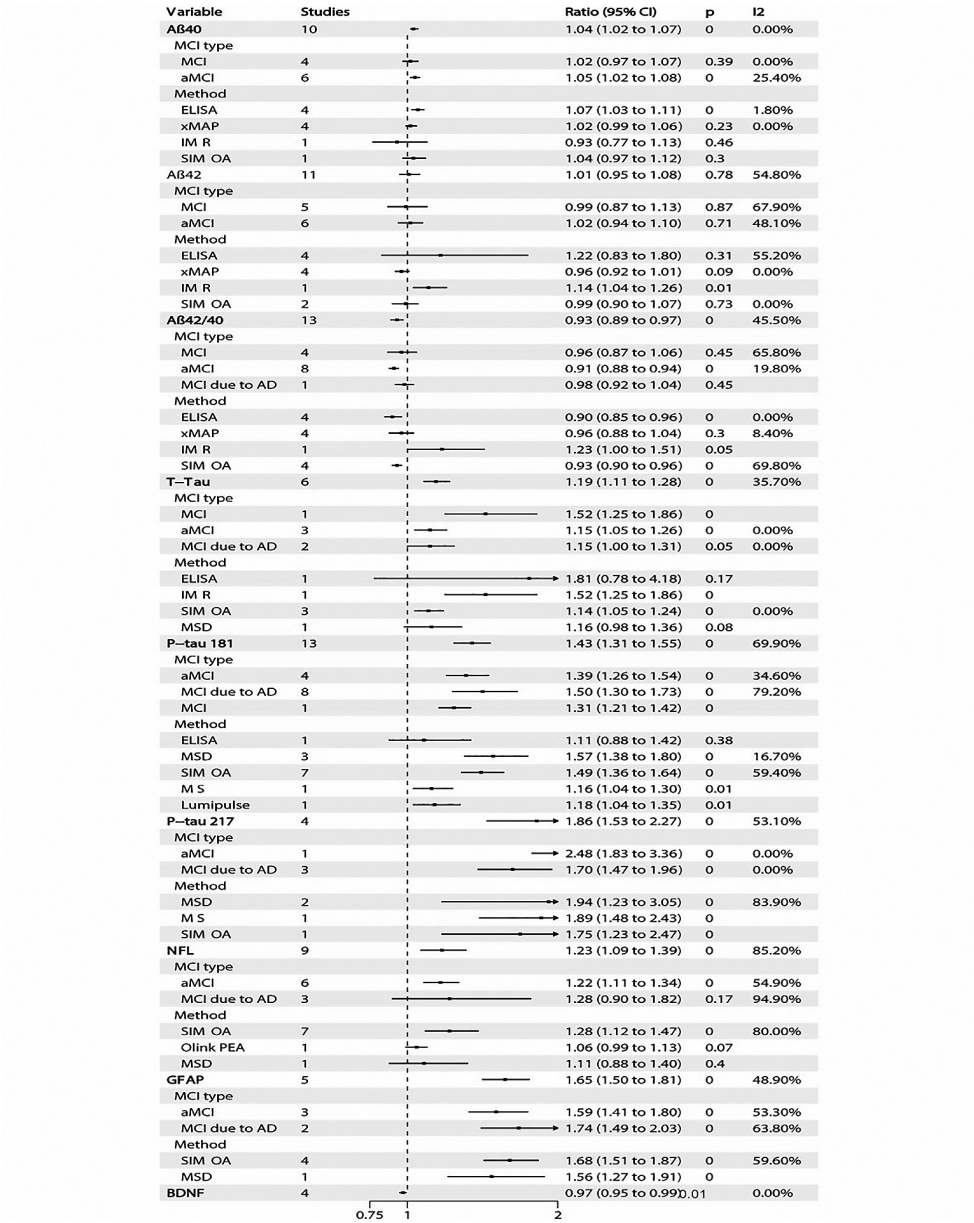

Figure 2. MCI converters to MCI non-converters ratio of blood biomarkers.

3.2.2. Relative risks of blood biomarkers

Relative risks (RR) of plasma Aβ42, Aβ42/Aβ40, P-tau, NFL, and APOE were pooled as continuous or categorical variables in 22 articles **(Figure 3, Supplementary Fig. 10-13).** P-tau (RR=2.50, 95%CI: 2.04-3.06) as a continuous variable, Aβ42/Aβ40 (RR=1.28, 95%CI: 1.01-1.61) as a categorical variable can predict the conversion from MCI to AD. Aβ42/Aβ40 (RR=0.97, 95%CI: 0.84-1.13), NFL (RR=1.20, 95%CI: 0.78-1.85) as continuous variables, Aβ42 (RR=1.01, 95%CI: 0.74-1.39) as categorical variable couldn't predict the status conversion of MCI. Besides, APOE (RR=1.03, 95%CI: 0.89-1.19) couldn't predict MCI conversion either.

When it comes to specific MCI types, continuous P-tau could predict the conversion of either aMCI (RR=2.152, 95%CI: 1.661-2.788) or MCI (RR=3.188, 95%CI: 2.29-4.439). However, categorical Aβ42/Aβ40 could neither predict the conversion of sole aMCI group (RR=1.37, 95%CI: 0.944-1.987) nor the conversion of the sole MCI group (RR=1.222, 95%CI: 0.912-1.636).

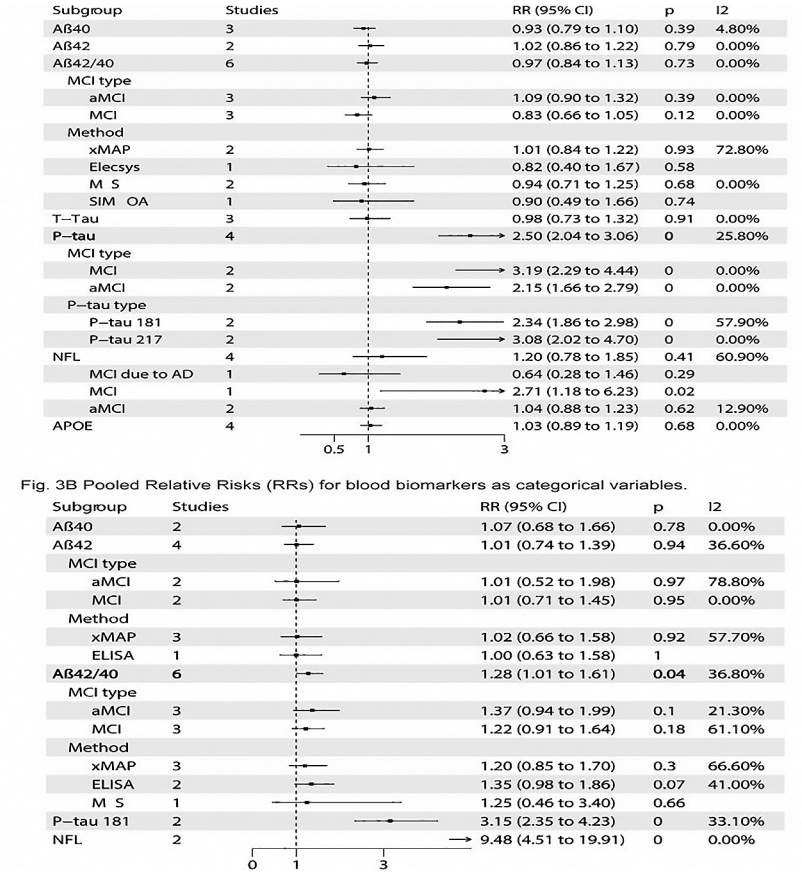

Fig. 3B Pooled Relative Risks (RRs) for blood biomarkers as categorical variables.

Figure 3. Pooled relative risks (RRs) for blood biomarkers as continuous or categorical variables.

3.2.3. Diagnostic performance of blood biomarkers

Diagnostic indexes of Aβ42/Aβ40, P-tau 181, P-tau 217, NFL, and GFAP were pooled in 12 articles **(Figure 4, Supplementary Fig. 14-22).** The HSROC curves of the pooled results demonstrated that the diagnostic efficacy of Aβ42/Aβ40 (P=0.102), P-tau 181 (P=0.788), P-tau 217 (P=0.978), NFL (P=0.579) was not impacted by threshold values. However, the diagnostic efficacy of GFAP was influenced by the threshold effect (P=0.000). For Aβ42/Aβ40, the pooled sensitivity and specificity were 86% (95% CI: 0.80-0.91) and 49% (95% CI: 0.25-0.73), respectively. The pooled PLR and NLR were 1.7 and 0.28, respectively. The pooled DOR was 6 (95% CI: 3-13), with an AUC of 0.84 (95% CI: 0.81-0.87). For P-tau 181, the pooled sensitivity

and specificity were 81% (95%CI: 0.74-0.87) and 78% (95%CI: 0.70-0.84), respectively. The pooled PLR and NLR were 3.6 and 0.24, respectively. The pooled DOR was 15 (95% CI: 10-23), with an AUC of 0.86 (95% CI: 0.83-0.89). For P-tau 217, the pooled sensitivity and specificity were 91% (95%CI: 0.85-0.94) and 81% (95%CI: 0.76-0.86), respectively. The pooled PLR and NLR were 4.9 and 0.12, respectively. The pooled DOR was 42 (95% CI: 21-81), with an AUC of 0.93 (95% CI: 0.91-0.95). For NFL, the pooled sensitivity and specificity were 80% (95%CI: 0.69-0.87) and 61% (95%CI: 0.46-0.75), respectively. The pooled PLR and NLR were 2.1 and 0.33, respectively. The pooled DOR was 6 (95% CI: 3-13), with an AUC of 0.80 (95% CI: 0.76-0.83). For GFAP, the pooled sensitivity and specificity were 71% (95%CI: 0.63-0.79) and 86% (95%CI: 0.81-0.91), respectively. The pooled PLR and NLR were 4.33 and 0.39, respectively. The pooled DOR was 12.71 (95% CI: 7.71-22.54), with an AUC of 0.84 (95% CI: 0.78-0.90). The Deek's funnel plot asymmetry test results did not show publication bias for the above five biomarkers (Aβ42/Aβ40: P=0.860; P-tau 181: P=0.893; P-tau 217: P=0.470; NFL: P=0.426; GFAP: P=0.801). In subgroup analysis by MCI type, Aβ42/Aβ40 had higher sensitivity and specificity in aMCI than MCI, while NFL had higher sensitivity and specificity in MCI than aMCI **(Supplementary material 6).**

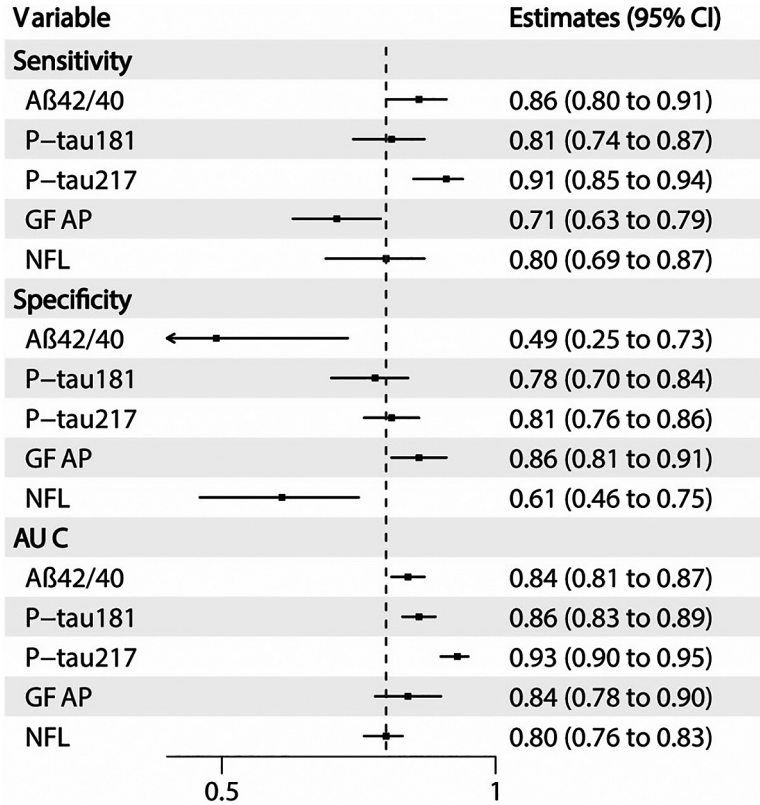

Figure 4. Pooled sensitivity, specificity, and AUC for blood biomarkers in predicting MCI conversion.

3.2. Subgroup analysis, meta-regression, sensitivity analysis, and publication bias

Heterogeneity existed among Aβ42, Aβ42/Aβ40, P-tau181, P-tau217, NFL and GFAP in ROM, NFL in continuous RR, Aβ42/Aβ40, P-tau181 and NFL in diagnostic analyses. Subgroup analyses **(Supplementary Fig. 23-59)** showed that baseline MMSE, female percentage, APOE carries and region might be the sources of heterogeneity for P-tau 217 in ROM, baseline MMSE, age and follow-up duration for GFAP in ROM, study type, region and MCI type for RR of NFL as continuous variables. For diagnostic results, APOE *ε4* carriers and study type for Aβ42/Aβ40, study type for P-tau 181, and follow-up duration for NFL are potential factors

bringing about heterogeneity, as demonstrated by meta-regression results **(Supplementary material 5).** Sources of heterogeneity have not been found for Aβ42, Aβ42/Aβ40, P-tau 181, and NFL in ROM. However, the stability of the pooled ratios for P-tau 181 and NFL was stable, whereas unstable for Aβ42 and Aβ42/Aβ40 after sensitivity analyses **(Supplementary Fig. 60-68).** The heterogeneity of Aβ42, Aβ42/Aβ40 (I^2=54.8% P=0.015; I^2=45.5% P=0.03) has decreased but was still significant after removing an article (Ma 2011). In a new round of subgroup analysis, baseline MMSE and female percentage for Aβ42, baseline age and female percentage for Aβ42/Aβ40 contributed to the heterogeneity. Meanwhile, the pooled result of Aβ42 and Aβ42/Aβ40 became stable after sensitivity analyses. In the end, trim-and-fill method **(Supplementary Fig. 69-73)** indicated that the pooled RRs of continuous NFL and categorical Aβ42/Aβ40 were unstable. Therefore, the pooled results should be interpreted with caution. Publication bias **(Supplementary Fig. 74-93)** was found among P-tau181 (P=0.041) in ROM. Nevertheless, the effect size of P-tau181 was not influenced after implementing the trim-and-fill method.

3.3. Qualitative review

A total of 80 biomarkers without sufficient data to carry out meta-analysis were summarized here. Under the ATNIVS frame **(Table 2),** categorical P-tau 181 and NFL can predict the risk of MCI conversion, while continuous Aβ42, Aβ40, and categorical Aβ40 could not **(Figure 3).** However, caution is needed in case of over-interpretation, given the limited number of included studies.

For other blood biomarkers, continuous T-tau couldn't predict MCI conversion **(Figure 3A).** Higher coated platelet levels, beta-secretase 1 (BACE1) activity, cortisol, APOA-II, soluble TREM2 (sTREM2), sTNFR1, CCL23, IL-17A, mid regional proadrenomedullin (MR-ProADM), midregional proatrial natriuretic peptide (MR-ProANP), nonceruloplasmin copper, miR-146a, miR-181a, lower APP ratio (APPr), intracellular calcium-independent PLA2 (iPLA2), complement C3 (CC3), complement factor I (CFI), CCL11, not dissociated Aβ42 autoantibodies, HSV-1 specific antibodies, epidermal growth factor (EGF), neural growth factor (NGF), TSH, 24-hydroxycholesteryl esters (24OH-CE), miR206, ceruloplasmin, selenoprotein P and caffeine were related with increased risk of MCI conversion. Nevertheless, the predictive performance of some BBMs such as APOA-I, clusterin, total cholesterol, homocysteine, cystatin C, CRP, complement factor H (CFH), transthyretin, pancreatic prohormone, uric acid, MDA, Ficolin-2, serum calcium, miR132 and alpha-2-macrogloblin (A2M) remained underdetermined due to contradictory results from insufficient research. Notably, neuronal-derived exosome (NDE) is an emerging candidate in the diagnosis and prognosis of AD. Lower levels of Aβ1–42 in plasma NDEs predict MCI conversion with an AUC of 0.84. Besides, plasma NDE levels of P-S396-tau, repressor element 1-silencing transcription factor (REST), and neurogranin (NRGN) take on remarkable discrimination of MCI-converters and MCI-nonconverters.

Furthermore, proteomics and metabolomics uncover the potential values of other blood biomarkers. For proteomics, inflammation/chemotaxis (IL-8, CSF-1, CCL23, CX3CL1, CXCL and TNFRSF12A),

Biomarker category	Higher	Lower	Undetermined
Core biomarkers			
A (Aβ proteinopathy)	BACE1 activity	Appr	clusterin, A2M
T (AD tau proteinopathy)	categorical P-tau 181	—	—
Non-specific biomarkers of tissue reaction involved in AD pathophysiology			
N (injury, dysfunction, or degeneration of neuropil)	categorical NFL	—	—
I (inflammation)	sTREM2, sTNFR1, CCL23, IL-17A	iPLA2, CC3, CFI, CCL11	CRP, CFH
Biomarkers of non-AD co-pathology			
V vascular brain injury	MR-ProADM, MR-ProANP	—	—
S α-syn	—	—	—

Table 2. Blood biomarkers included in qualitative review.

extracellular matrix remodeling (TIMP-4 and MMP-3), endothelial injury (VEGF-A and NOS3), lipid metabolism (PHOSPHO1) and insulin-like growth factor signaling regulation (IGFBP2), proprotein convertase subtilisin/kexin type 7 (PCSK7), ephrin receptor tyrosine kinase A2 (EFNA2), AP-1 complex subunit gamma-like 2 (AP-1) , and collagen alpha1 (XV) chain (COL15A1) were reported to be related to MCI conversion. For metabolomics, 2,4-dihydroxybutanoic acid (MC1), Unidentified carboxylic acid (MC2), PC aa C38:4, PC ae C36:2, PC ae C40:3, PC ae C42:4, PC ae C44:4, PC ae C44:4, SM C16:0, SM C18:1, SM (OH) C14:1, SM C20:2, polyamine and l-arginine metabolism were implicated in the conversion. Collectively, plentiful blood biomarkers hold the potential to predict MCI conversion. However, more validation studies are warranted.

4. DISCUSSION

In the present study, we conducted a comprehensive systematic review and meta-analysis aiming to evaluate the predictive effects of blood biomarkers in the conversion from MCI to AD. Our study first demonstrated that baseline levels of Aβ40, Aβ42/Aβ40, T-tau, P-tau 181, P-tau 217, NFL, and GFAP were discrepant among MCI converters from MCI non-converters by analyzing pooled ratio of means. Secondly, we found baseline continuous P-tau, categorical Aβ42/Aβ40, could predict the future conversion risk of MCI by pooling RRs. Thirdly, diagnostic meta-analyses exhibited that Aβ42/Aβ40, P-tau 181, NFL, and GFAP exhibited superior value, while P-tau 217 manifested remarkable value in predicting MCI conversion to AD.

Plasma Aβ42/Aβ40 is associated with CSF Aβ42/Aβ40 and Aβ-PET and is more valuable in predicting conversion to MCI or AD in cognitively unimpaired (CU) people than Aβ42 or Aβ40 alone. Alternatively, plasma Aβ42/Aβ40 has been completely altered in the pre-symptomatic stage of AD, rendering it possible to accurately identify Aβ pathology in CU people (Palmqvist *et al.*, 2019). Our pooled results suggested lower Aβ42/Aβ40 and higher Aβ40 in MCI-c compared to MCI-nc, which were discordant with a former meta-analysis (Qu *et al.*, 2021). Possible explanations were that we included more recent studies and removed one study that brought significant heterogeneity (Fei, Jianghua, Rujuan, Wei, & Qian, 2011). Nevertheless, aligning with Li *et al.*, (Li, Ma, Tan, & Yu, 2022), we found that categorical Aβ42/Aβ40 could predict future MCI conversion. In diagnostic performances, the DOR of Aβ42/Aβ40 is 6, which is lower than P-tau 217, P-tau 181, GFAP, suggesting that Aβ42/Aβ40 might not be that sensitive to the early progression of Alzheimer's continuum, and it might have reached a plateau at preclinical AD (Yakoub *et al.*, 2023) Besides, its specificity requires improving. Moreover, the predictive performances of plasma Aβ42/Aβ40 were lower than CSF Aβ42/Aβ40 (Li *et al.*, 2022). The possible explanations are as follows. Firstly, the stickiness of Aβ hinders its flow into the bloodstream, and its transportation mechanisms remain unclear. Secondly, detecting soluble Aβ in plasma is challenging due to blood dilution, and its level decreases as AD progresses. Thirdly, derived from the APP protein, Aβ is not only confined to the CNS and but also serves physiological functions, including antimicrobial roles, rendering peripheral Aβ production and clearance complex. At last, the amphipathic structure of Aβ causes it to bind to various proteins and blood cells (Huang, Wang, & Guo, 2022).

As well-known, the advent of blood P-tau seems to have altered the landscape of AD diagnosis and prognosis since it increases with Aβ accumulation and clinical severity in patients rather than in individuals with non-AD induced cognitive impairment (Karikari *et al.*, 2022). Moreover, even in people without Aβ pathologic deposits at baseline, P-tau 231 and P-tau 217 were in close relation to a longitudinal increase in Aβ-PET uptake. Chronologically, P-tau181 continued to rise as CDR scores went from 0 to 3, but did not reach abnormal levels until 6.5 and 5.7 years after abnormalities CSF Aβ and Aβ-PET, respectively (Moscoso *et al.*, 2021), whereas alterations of plasma P-tau 231 and P-tau217 occurred before the appearance of pathological Aβ plaques, thus reflecting early brain Aβ changes earlier. Thus, plasma P-tau 231 and P-tau 217 are earlier biomarkers indicating Aβ changes than P-tau 181. Particularly, P-tau231, may be the earliest abnormal blood p-tau of AD (Ashton *et al.*, 2022; Milà-Alomà *et al.*, 2022). However, in our current review, only one study investigated the predictive performance of P-tau 231 in MCI conversion (Janelidze, Bali, *et al.*, 2023) (sensitivity: 0.87; specificity: 0.69; AUC:75%). Besides, it might have also reached a plateau at preclinical AD. Therefore, further studies of P-231 are warranted (Yakoub *et al.*, 2023). Interestingly, plasma P-tau181 and P-tau217 have been consecutively

reported to accurately predict cognitive deterioration and conversion to AD dementia in the next 2-6 years in MCI patients (Hansson *et al.*, 2022). In consistent with previous studies, our pooled results also attested to the predictive ability of P-tau 181 and P-tau 217. Given that P-tau 217 has the largest relative increase (250%-600%) in AD compared to other non-AD neurodegenerative diseases (Thijssen *et al.*, 2021), it might be the most sensitive blood biomarker to detect MCI conversion, which was further proved by its pooled sensitivity, specificity and DOR. Nonetheless, although plasma P-tau has gained momentum in the timely diagnosis of AD, it can elevate various comorbidities (such as chronic kidney disease, hypertension, etc.), giving rise to false positives (Mielke *et al.*, 2022). Fortunately, a recent study indicated that applying P-tau/T-tau could mitigate the impacts on kidney function (Janelidze, Barthélemy, He, Bateman, & Hansson, 2023).

As for T-tau, the overlap of T-tau between diagnostic groups is considerable, which has limited its diagnostic value. The correlation between T-tau levels in blood and CSF was also poor, indicating that the majority of T-tau in the blood is of peripheral origin. In contrast, the central origin is relatively small (about 20%), making it impossible to detect ongoing neurodegeneration. Nevertheless, high baseline levels of T-tau often predicted faster cognitive decline (Karikari *et al.*, 2022), which was further corroborated by our finding that MCI converters have higher baseline T-tau than MCI non-converters.

Unlike other blood biomarkers of AD, serum GFAP (a marker of reactive astrocyte hyperplasia) is far superior to CSF GFAP in determining the pathological exacerbation of brain Aβ (Benedet *et al.*, 2021) since periodic freeze-thaw has a significant effect on the concentration of CSF GFAP rather than serum GFAP (Simrén, Weninger, *et al.*, 2022). Serum GFAP begins to rise in preclinical AD and is correlated with AD incidence over 10 years before diagnosis (9-17 years). P-tau181 and NfL were related to moderate AD risk (up to 9 years), suggesting that GFAP might be an earlier biomarker before P-tau181 and NFL for AD (Stocker *et al.*, 2023), which has also been confirmed by recent studies (Milà-Alomà *et al.*, 2022). Besides, serum GFAP can also distinguish AD from frontotemporal dementia, and predict the cognitive decline of CU (Hansson *et al.*, 2022) and the transition of MCI to dementia (Oeckl *et al.*, 2022). Therefore, plasma GFAP seems to be a very promising biomarker. The present findings also disclosed higher GFAP in MCI converters and higher DOR compared to NFL and Aβ42/Aβ40.

As a marker of nerve axon injury, NFL can be detected simultaneously in CSF and plasma (serum), and is currently the most promising marker of neurodegeneration. In cognitively normal people, plasma NFL increases markedly with age and becomes more pronounced after age 65 (Simrén, Andreasson, *et al.*, 2022). Although NFL is weak as a diagnostic biomarker relative to P-tau 181 or P-tau 231, above-threshold NFL levels predict faster cognitive decline (Smirnov *et al.*, 2022). The pooled ROMs indicated higher NFL in MCI converters, yet pooled RRs suggested no predictive effects of NFL, which contradicted Li *et al.*, (Li *et al.*, 2022). The reasons for these discrepancies might be that we concentrated mainly on MCI conversion, while Li *et al.* focused on the whole AD continuum. Ultimately, it's worth noting that age has an increasing impact on serum NFL levels, while other factors such as kidney function and blood volume also have some effects (Koini *et al.*, 2021) among people over 60 years old.

Generally, given that MCI is multifactorial in etiology and heterogeneous in clinical presentation, the predictive value of single biomarkers tends to be limited. Therefore, the combination of different BBMs or of BBMs with biomarkers from other easily accessible categories might contain giant potential. It's reported that amnestic MCI patients with hAT (lower plasma Aβ42/Aβ40 and higher p-tau181) had 4.83 times the risk for AD conversion (HR=4.83, 95% CI 2.37–9.86, P<0.001) compared to patients with lAT (higher plasma Aβ42/Aβ40 and lower p-tau181) (Xiao *et al.*, 2022). Plasma P-tau 217 combined with cognitive tests and APOE ε4 status forecasted the conversion to AD in MCI patients with high accuracy (AUC: 0.89, 95%CI: 0.83-0.94) (Janelidze *et al.*, 2020; Palmqvist *et al.*, 2022).

Limitations in our meta-analysis should be acknowledged. First, sources of heterogeneity still couldn't be found after meta-regression and subgroup analysis for P-tau 181 and NFL in ROM. Other variables (e.g., education years, adjustments, and medications) should also be considered in future studies. In addition, data extraction might bring some heterogeneity. Specifically, some studies reported log-transformed value; some reported median (IQR), while there are a handful of studies whose data couldn't be directly extracted from articles

nor attained from the authors, which could only be manually acquired from figures. Secondly, current studies were relatively few and lacked detailed information such as capture antibodies. Therefore, the results of subgroup analysis should be interpreted with caution. Meanwhile, the predictive performances of some biomarkers might be underestimated due to insufficient research. More studies were warranted to validate our results. Last but not least, included studies are primarily conducted by some cohorts utilizing retrospective samples in specialized centers. Prospective validation and inclusion of particular types of MCI are necessary for future research.

5. CONCLUSION

This meta-analysis has discussed the predictive role of blood biomarkers in the conversion from MCI to AD, which will facilitate the clinical implementation of blood biomarkers soon. Of note, the predictive effects may vary with MCI types, as well as measuring methods. Therefore, more prospective cohorts based on particular MCI and high-sensitivity assays are needed to validate our current results.

Acknowledgments

None.

Conflict of Interest Disclosures

The authors declare no conflict of interest.

Funding

This work was supported by Brain Science and Brain-Like Intelligence Technology of the Ministry of Science and Technology of China (2021ZD0201804).

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author upon reasonable request.

LIST OF ABBREVIATIONS

Abbreviation	Full name
24OH-CE	24-Hydroxycholesteryl Esters
A2M	alpha-2-macrogloblin
Aβ	amyloid-β
AD	Alzheimer's disease
APOA-II	apolipoprotein-II
APOE	apolipoprotein E
APP	amyloid precursor protein
BACE1	beta-site amyloid precursor protein cleaving enzyme 1
BBM	blood biomarkers
BDNF	brain-derived neurotrophic factor
CXCL	chemokine (C-X-C motif) ligand
EGF	epidermal growth factor
GFAP	glial fibrillary acidic protein
iPLA2	intracellular calcium-independent PLA2
IGFBP2	insulin-like growth factor signaling regulation
MR-ProADM	midregional proadrenomedullin
MR-ProANP	midregional proatrial natriuretic peptide
NDE	neuronal-derived exosome
NFL	neurofilament light
NGF	neural growth factor

Abbreviation	Full name
NRGN	neurogranin
p-tau	phosphorylated tau
PCSK7	proprotein convertase subtilisin/kexin type 7
REST	repressor element 1-silencing transcription factor
sTNFR1	soluble tumor necrosis factor α receptor 1
sTREM2	soluble form of triggering receptor expressed on myeloid cells 2
t-tau	total tau
TNFRSF12A	TNF receptor superfamily member 12A

REFERENCES

Alzheimer's disease facts and figures. [J]. Alzheimers Dement, 2023, 19(4): 1598-1695.

Albert, M. S., DeKosky, S. T., Dickson, D., *et al*. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease [J]. Alzheimers Dement, 2011, 7(3): 270-279.

Ashton, N. J., Janelidze, S., Mattsson-Carlgren, N., *et al*. Differential roles of Aβ42/40, p-tau231 and p-tau217 for Alzheimer's trial selection and disease monitoring [J]. Nat Med, 2022, 28(12): 2555-2562.

Barthélemy, N. R., Horie, K., Sato, C., *et al*. Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease [J]. J Exp Med, 2020, 217(11).

Benedet, A. L., Milà-Alomà, M., Vrillon, A., *et al*. Differences Between Plasma and Cerebrospinal Fluid Glial Fibrillary Acidic Protein Levels Across the Alzheimer Disease Continuum [J]. JAMA Neurol, 2021, 78(12): 1471-1483.

Bilgel, M., An, Y., Walker, K. A., *et al*. Longitudinal changes in Alzheimer's-related plasma biomarkers and brain amyloid [J]. Alzheimers Dement, 2023.

Fei, M., Jianghua, W., Rujuan, M., *et al*. The relationship of plasma Aβ levels to dementia in aging individuals with mild cognitive impairment [J]. J Neurol Sci, 2011, 305(1-2): 92-96.

Friedrich, J. O., Adhikari, N. K., & Beyene, J. The ratio of means method as an alternative to mean differences for analyzing continuous outcome variables in meta-analysis: a simulation study [J]. BMC Med Res Methodol, 2008, 8: 32.

Hampel, H., Cummings, J., Blennow, K., *et al*. Developing the ATX(N) classification for use across the Alzheimer disease continuum [J]. Nat Rev Neurol, 2021, 17(9): 580-589.

Hansson, O., Edelmayer, R. M., Boxer, A. L., *et al*. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease [J]. Alzheimers Dement, 2022, 18(12): 2669-2686.

Huang, S., Wang, Y. J., & Guo, J. Biofluid Biomarkers of Alzheimer's Disease: Progress, Problems, and Perspectives [J]. Neurosci Bull, 2022, 38(6): 677-691.

Jack, C. R., Jr., Bennett, D. A., Blennow, K., *et al*. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease [J]. Alzheimers Dement, 2018, 14(4): 535-562.

Janelidze, S., Bali, D., Ashton, N. J., *et al*. Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease [J]. Brain, 2023, 146(4): 1592-1601.

Janelidze, S., Barthélemy, N. R., He, Y., *et al*. Mitigating the Associations of Kidney Dysfunction With Blood Biomarkers of Alzheimer Disease by Using Phosphorylated Tau to Total Tau Ratios [J]. JAMA Neurol, 2023, 80(5): 516-522.

Janelidze, S., Mattsson, N., Palmqvist, S., *et al*. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia [J]. Nat Med, 2020, 26(3): 379-386.

Karikari, T. K., Ashton, N. J., Brinkmalm, G., *et al*. Blood phospho-tau in Alzheimer disease: analysis, interpretation, and clinical utility [J]. Nat Rev Neurol, 2022, 18(7): 400-418.

Koini, M., Pirpamer, L., Hofer, E., *et al*. Factors influencing serum neurofilament light chain

levels in normal aging [J]. Aging (Albany NY), 2021, 13(24): 25729-25738.

Li, R. X., Ma, Y. H., Tan, L., *et al*. Prospective biomarkers of Alzheimer's disease: A systematic review and meta-analysis [J]. Ageing Res Rev, 2022, 81: 101699.

McInnes, M. D. F., Moher, D., Thombs, B. D., *et al*. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement [J]. Jama, 2018, 319(4): 388-396.

McKhann, G., Drachman, D., Folstein, M., *et al*. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease [J]. Neurology,1984, 34(7): 939-944.

McKhann, G. M., Knopman, D. S., Chertkow, H., *et al*. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease [J]. Alzheimers Dement, 2011, 7(3): 263-269.

Mielke, M. M., Dage, J. L., Frank, R. D., *et al*. Performance of plasma phosphorylated tau 181 and 217 in the community [J]. Nat Med, 2022, 28(7): 1398-1405.

Milà-Alomà, M., Ashton, N. J., Shekari, M., *et al*. Plasma p-tau231 and p-tau217 as state markers of amyloid-β pathology in preclinical Alzheimer's disease [J]. Nat Med, 2022, 28(9): 1797-1801.

Moscoso, A., Grothe, M. J., Ashton, N. J., *et al*. Time course of phosphorylated-tau181 in blood across the Alzheimer's disease spectrum [J]. Brain, 2021, 144(1): 325-339.

Oeckl, P., Anderl-Straub, S., Von Arnim, C. A. F., *et al*. Serum GFAP differentiates Alzheimer's disease from frontotemporal dementia and predicts MCI-to-dementia conversion [J]. J Neurol Neurosurg Psychiatry, 2022.

Olsson, B., Lautner, R., Andreasson, U., *et al*. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis [J]. Lancet Neurol, 2016, 15(7): 673-684.

Palmqvist, S., Janelidze, S., Stomrud, E., *et al*. Performance of Fully Automated Plasma Assays as Screening Tests for Alzheimer Disease-Related β-Amyloid Status [J]. JAMA Neurol, 2019, 76(9): 1060-1069.

Palmqvist, S., Stomrud, E., Cullen, N., *et al*. An accurate fully automated panel of plasma biomarkers for Alzheimer's disease [J]. Alzheimers Dement, 2022.

Petersen, R. C. Mild cognitive impairment as a diagnostic entity [J]. J Intern Med, 2004, 256(3): 183-194.

Qu, Y., Ma, Y. H., Huang, Y. Y., *et al*. Blood biomarkers for the diagnosis of amnestic mild cognitive impairment and Alzheimer's disease: A systematic review and meta-analysis [J]. Neurosci Biobehav Rev, 2021, 128: 479-486.

Simrén, J., Andreasson, U., Gobom, J., *et al*. Establishment of reference values for plasma neurofilament light based on healthy individuals aged 5-90 years [J]. Brain Commun, 2022, 4(4): fcac174.

Simrén, J., Weninger, H., Brum, W. S., *et al*. Differences between blood and cerebrospinal fluid glial fibrillary Acidic protein levels: The effect of sample stability [J]. Alzheimers Dement, 2022, 18(10): 1988-1992.

Smirnov, D. S., Ashton, N. J., Blennow, K., *et al*. Plasma biomarkers for Alzheimer's Disease in relation to neuropathology and cognitive change [J]. Acta Neuropathol, 2022, 143(4): 487-503.

Stang, A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses [J]. Eur J Epidemiol, 2010, 25(9): 603-605.

Stocker, H., Beyer, L., Perna, L., *et al*. Association of plasma biomarkers, p-tau181, glial fibrillary acidic protein, and neurofilament light, with intermediate and long-term clinical Alzheimer's disease risk: Results from a prospective cohort followed over 17 years [J]. Alzheimers Dement, 2023, 19(1): 25-35.

Teunissen, C. E., Verberk, I. M. W., Thijssen, E. H., *et al*. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation [J]. Lancet Neurol, 2022, 21(1): 66-77.

Thijssen, E. H., La Joie, R., Strom, A., *et al*. Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study [J]. Lancet Neurol, 2021, 20(9): 739-752.

Wang, J. T., Xu, G., Ren, R. J., *et al*. The impacts of health insurance and resource on the burden of Alzheimer's disease and related dementias in the world population [J]. Alzheimers Dement, 2022.

Wang, Z. B., Tan, L., Wang, H. F., *et al*. Differences between ante mortem Alzheimer's disease biomarkers in predicting neuropathology at autopsy [J]. Alzheimers Dement, 2023.

Xiao, Z., Wu, W., Ma, X., *et al*. Plasma Aβ42/Aβ40 and p-tau181 Predict Long-Term Clinical Progression in a Cohort with Amnestic Mild Cognitive Impairment [J]. Clin Chem, 2022, 68(12): 1552-1563.

Yakoub, Y., Ashton, N. J., Strikwerda-Brown, C., *et al*. Longitudinal blood biomarker trajectories in preclinical Alzheimer's disease [J]. Alzheimers Dement, 2023.

SUPPLEMENTARY MATERIALS

Supplementary material 1: PRISMA checklist
Supplementary material 2: Search strategy
Supplementary material 3: References for included 89 studies
Supplementary material 4: Included studies for pooled ROMs, RRs, and diagnostic indexes
Supplementary material 5: NOS score for studies included in meta-analysis
Supplementary material 6: Meta regression