Engineering and Scientific International Journal (ESIJ)
Volume 13, Issue 3, July – September 2026
ISSN 2394-7187(Online)
ISSN 2394 - 7179 (Print)

Cerebrospinal Fluid Biomarkers in the Workup of Cognitive Symptoms: A Four Year Prospective Cohort: Diagnostic Reclassification and Predictive Performance of ATN Profiling in Memory Clinic Patients

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Abstract — Cerebrospinal fluid (CSF) biomarkers for amyloid-beta (Aβ42, Aβ42/Aβ40 ratio) and tau (total tau, phospho-tau-181) have transformed the diagnostic workup of cognitive symptoms by enabling in-vivo characterisation of underlying Alzheimer pathology. The ATN classification framework amyloid (A), tau (T), and neurodegeneration (N) has emerged as the operational structure for biomarker interpretation. We undertook a prospective cohort study of 224 patients with cognitive symptoms referred for CSF biomarker testing at a tertiary memory clinic, with 4-year follow-up to characterise diagnostic reclassification rates, conversion trajectories, and predictive performance of the ATN framework. The A+T+ profile was identified in 96 patients (42.9%), A+T- in 32 (14.3%), A-T+ in 22 (9.8%), and A-T- in 54 (24.1%). The remaining 20 patients (8.9%) had indeterminate samples. CSF biomarkers led to diagnostic reclassification in 68 patients (30.4%), most commonly from probable AD to non-AD (removal of an AD label in patients with A-T- profile) or from non-specific MCI to prodromal AD (A+T+ profile). Cumulative dementia conversion at 4 years was 55% in A+T+ MCI patients compared with 17% in A-T- MCI patients. Strongest independent predictors of conversion included biomarker profile, lower baseline MoCA, hippocampal atrophy, APOE ε4 status, and advanced age. The findings support routine CSF biomarker assessment in suspected early Alzheimer disease.

Keywords — *Alzheimer's Disease; CSF Biomarkers; Amyloid-Beta; Phospho-Tau; ATN Classification; Mild Cognitive Impairment; Dementia Conversion*

1. Introduction

Alzheimer's disease has historically been a clinical diagnosis supported by neuropsychological testing and structural imaging, with definitive characterisation requiring post-mortem examination. The introduction of validated cerebrospinal fluid biomarkers Aβ42, the Aβ42/Aβ40 ratio, total tau, and phospho-tau-181 has fundamentally changed this picture. These biomarkers permit in-vivo characterisation of the molecular pathology underlying cognitive symptoms with sensitivity and specificity each exceeding 85% in validation studies against neuropathological gold standards. The ATN classification framework, formalised in 2018 consensus criteria, has emerged as the operational structure for biomarker interpretation: A for amyloid (using CSF or amyloid PET), T for tau (using CSF phospho-tau or tau PET), and N for neurodegeneration (using CSF total tau, MRI, or FDG-PET). Clinical implementation of CSF biomarker testing in South Asian tertiary memory clinics has lagged behind Western centres, with cost, infrastructure, and clinician familiarity all contributing. As anti-amyloid disease-modifying therapies (aducanumab, lecanemab, donanemab) move from clinical trials into approved practice, accurate identification of patients with underlying Alzheimer pathology becomes practically important: these therapies are only indicated in patients with confirmed amyloid pathology, and CSF testing or amyloid PET represents the principal means of confirmation (Jha, Kumar,, & Neha, 2026; Kumar, Gautam,, & Maitiy, 2026; Bhatnagar, Kumar,, & Shivam, 2026). We undertook a prospective cohort study at our tertiary memory clinic to characterise the experience of routine CSF biomarker testing in patients with cognitive symptoms. Specific objectives were to describe the ATN profile distribution in our population, document diagnostic reclassification rates following biomarker testing, characterise 4-year clinical trajectories stratified by biomarker profile, and identify independent predictors of dementia conversion that could inform clinical decision-making and patient counselling (Yatish, Khatoon,, & Kumar, 2026; Aneeshkumar & JothiVenkateswaran, 2015; Kumar, Gautam,, & Maitiy, 2026).

2. Methods

We conducted a prospective cohort study at the memory clinic of a tertiary medical centre between January 2020 and December 2023, with follow-up extending to December 2024. Inclusion required (a) cognitive symptoms with at least one of subjective cognitive decline, mild cognitive impairment, or possible dementia by clinical assessment; (b)

DOI: 10.30726/esij/v13.i3.2026.1330040

ISSN 2394-7187(Online)
ISSN 2394 - 7179 (Print)

referral for CSF biomarker testing as part of the diagnostic workup; (c) age 40 or older; and (d) capacity to consent for longitudinal follow-up. Exclusion criteria included contraindications to lumbar puncture, severe dementia (MMSE <12), depression so severe that cognitive symptoms could not be evaluated, and active psychiatric disorders. The final cohort comprised 224 patients. CSF was obtained by lumbar puncture using standardised protocols including pre-procedure imaging review for intracranial pressure concerns, atraumatic needle technique, and collection in polypropylene tubes. Approximately 12 mL of CSF was obtained, with the first 1 mL discarded to minimise blood contamination. Samples were processed within 2 hours, aliquoted, and stored at -80°C until batched analysis. Aβ42, Aβ40, total tau, and phospho-tau-181 were measured by validated ELISA platforms with internal and external quality control. Cut-offs for positivity were defined by validation against an amyloid PET-positive reference cohort: Aβ42/Aβ40 ratio <0.064 (A+), phospho-tau-181 >27 pg/mL (T+). All patients underwent comprehensive clinical assessment including detailed history, neurological examination, cognitive testing (MMSE, MoCA, comprehensive neuropsychological battery), depression screening, and structural MRI. APOE genotyping was performed in patients consenting to additional sampling. ATN classification followed 2018 consensus criteria with operational definitions: A+ (amyloid biomarker positive, defined here by CSF Aβ42/Aβ40 ratio); T+ (tau biomarker positive, defined here by CSF phospho-tau); N+ (neurodegeneration, defined by hippocampal atrophy on MRI or elevated CSF total tau). The four-cell A×T classification is reported as the primary biomarker framework. Primary outcomes were diagnostic reclassification after biomarker testing (compared to pre-CSF clinical impression) and time to dementia conversion (defined as transition from MCI to clinical dementia using standard criteria) during 4-year follow-up. Patients with established dementia at baseline were excluded from conversion analyses. Secondary outcomes included treatment initiation patterns, family acceptability of the biomarker workup, and 4-year clinical trajectory summarised by composite cognitive-functional measures.

3. Results

3.1 Cohort Characteristics

Table 1. Baseline characteristics of the cognitive symptom cohort (n=224)

Characteristic	Value
Age, mean (SD), years	68.4 (8.6)
Female sex, n (%)	112 (50.0)
Years of formal education, mean (SD)	11.2 (5.4)
Education <8 years, n (%)	48 (21.4)
Pre-CSF clinical diagnosis: subjective cognitive decline, n (%)	42 (18.8)
Pre-CSF clinical diagnosis: MCI, n (%)	134 (59.8)
Pre-CSF clinical diagnosis: probable AD dementia, n (%)	32 (14.3)
Pre-CSF clinical diagnosis: non-AD dementia (FTD, LBD), n (%)	16 (7.1)
MMSE, mean (SD)	25.4 (3.6)
MoCA, mean (SD)	21.2 (4.4)
MoCA <22 (memory clinic suspicious threshold), n (%)	112 (50.0)
MRI hippocampal atrophy (visual rating ≥2), n (%)	98 (43.8)
MRI white matter hyperintensities (Fazekas ≥2), n (%)	82 (36.6)
APOE genotyping completed, n (%)	158 (70.5)
APOE ε4 carrier (≥1 allele), n (%)	68/158 (43.0)
APOE ε4/ε4 homozygote, n (%)	12/158 (7.6)
Family history of dementia, n (%)	78 (34.8)
Vascular risk factors ≥3, n (%)	112 (50.0)
Depression (PHQ-9 ≥10), n (%)	48 (21.4)
Functional impairment on FAQ, mean	8.4 (6.8)
Time from symptom onset to CSF testing, median, mo	18

3.2 ATN Profile Distribution

ATN biomarker profile distribution is shown in Figure 1. The classical A+T+ Alzheimer biomarker profile was identified in 96 patients (42.9%), and the A+T- profile indicating Alzheimer pathologic change without concurrent tau pathology was identified in a further 32 patients (14.3%). Together, A+ profiles indicating amyloid pathology accounted for 57.1% of the cohort. The A-T+ profile (suggesting non-AD tauopathy or alternative pathology) was identified in 22 patients (9.8%), and A-T- (no AD biomarker evidence) in 54 patients (24.1%). Twenty patients (8.9%) had indeterminate samples or borderline values not categorisable into clear ATN strata.

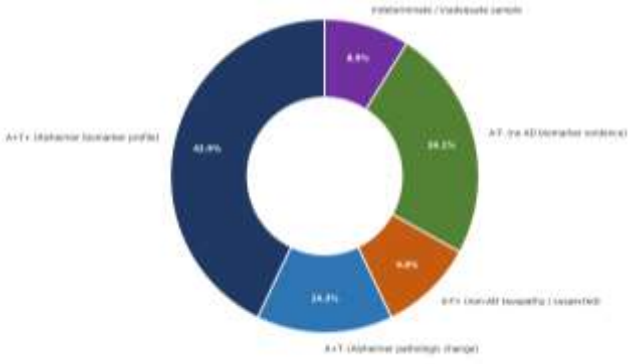

Fig.1: ATN biomarker classification distribution

Cluster analysis of CSF biomarker values (Figure 2) demonstrated the operational clarity of the A+/A- distinction. The A+ subgroup (encompassing both A+T+

DOI: 10.30726/esij/v13.i3.2026.1330040

ISSN 2394-7187(Online)
ISSN 2394 - 7179 (Print)

and A+T-) clustered at low Aβ42/Aβ40 ratios with elevated phospho-tau, while the A- subgroup clustered at higher Aβ42/Aβ40 ratios with lower phospho-tau. The clustering supports the validity of the binary A classification at the operational cut-offs used.

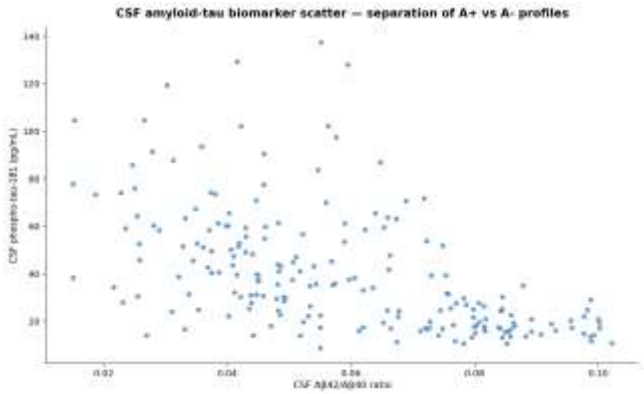

Fig.2: CSF amyloid-tau biomarker scatter

3.3 Diagnostic Reclassification

Table 2. Pre-CSF clinical diagnosis vs post-CSF biomarker-supported diagnosis

Pre-CSF diagnosis	n	A+ T+ post	A+ T- post	A- T+ post	A- T- post	Indeterm
Subjective cognitive decline	42	6	8	2	20	6
MCI (overall)	134	58	18	12	32	14
MCI with amnestic predominance	82	52	12	2	8	8
MCI non-amnestic	52	6	6	10	24	6
Probable AD dementia	32	28	4	-	-	-
Non-AD dementia syndrome	16	4	2	8	2	-
Diagnostic reclassification, n (%)	-	-	-	-	-	68 (30.4)
Among prob AD: reclassified to non-AD, n (%)	32	-	-	-	-	-
Among MCI: reclassified to prodromal AD, n (%)	134	58 (43.3)	-	-	-	-
Among SCD: reclassified to no AD pathology, n (%)	42	-	-	-	20 (47.6)	-

3.4 Trajectory by ATN Profile

Among patients with MCI at baseline (n=134), 4-year dementia conversion rates differed substantially by ATN profile (Figure 3). The A+T+ MCI subgroup showed the highest conversion rate, with approximately 55% progressing to clinical dementia by 4 years. The A+T- subgroup showed an intermediate conversion rate of approximately 40%. The A-T+ subgroup (suggesting non-AD pathology) showed approximately 32% conversion to various dementia syndromes including FTD and DLB. The A-T- MCI subgroup showed the lowest conversion rate at approximately 17%, with stabilisation or even mild improvement common among these patients.

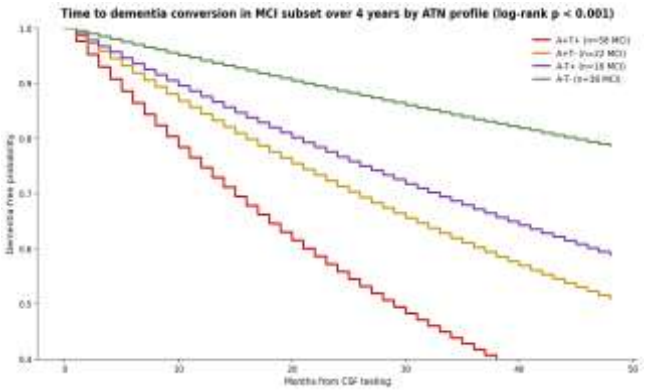

Fig.3: Time to dementia conversion in MCI subset over 4 years by ATN profile

Table 3. Four-year clinical trajectory by ATN profile (MCI patients, n=134)

Outcome	A+T+ (n=58)	A+T- (n=22)	A-T+ (n=16)	A-T- (n=38)
Converted to dementia, n (%)	32 (55.2)	8 (36.4)	4 (25.0)	6 (15.8)
Converted to AD-type dementia, n	30	6	-	2
Converted to other dementia type, n	2	2	4	4
Stable MCI at 4 years, n (%)	22 (37.9)	14 (63.6)	10 (62.5)	26 (68.4)
Reverted to normal cognition, n (%)	-	-	-	6 (15.8)
Mean annual MMSE decline	-1.8	-1.0	-0.8	-0.4
Mean annual MoCA decline	-2.4	-1.4	-1.2	-0.4
Initiated cholinesterase inhibitor, n (%)	42 (72.4)	12 (54.5)	6 (37.5)	2 (5.3)
Memantine added, n (%)	18 (31.0)	4 (18.2)	2 (12.5)	0 (0.0)
Anti-amyloid therapy initiated (where available)	8	2	-	-
Mortality during follow-up, n (%)	8 (13.8)	2 (9.1)	2 (12.5)	4 (10.5)

DOI: 10.30726/esij/v13.i3.2026.1330040

ISSN 2394-7187(Online)
ISSN 2394 - 7179 (Print)

3.5 Predictors of Dementia Conversion

Multivariable Cox regression identified ten independent predictors of progression to dementia within 4 years. The A+T+ biomarker profile carried by far the strongest single association (HR 6.42), followed by A+T- profile, low baseline MoCA, hippocampal atrophy on MRI, and APOE genotype with substantially elevated risk in homozygotes. Subjective cognitive decline (without MCI) was protective, as was active participation in a structured cognitive management programme. The strong performance of the biomarker variables, even after adjustment for clinical and imaging variables, supports the incremental information value of biomarker testing.

Table 4. Patient and family perspectives on biomarker testing

Domain	Patients agreeing, n (%) of 224
Felt biomarker testing was helpful for understanding	186 (83.0)
Reported reduced uncertainty about diagnosis	178 (79.5)
Found the lumbar puncture procedure tolerable	202 (90.2)
Post-LP headache lasting >24 hours	32 (14.3)
Post-LP headache requiring blood patch	2 (0.9)
Family member found result helpful for planning	178 (79.5)
Anxiety related to biomarker result reported	52 (23.2)
Genetic counselling recommended (APOE positive)	68 (30.4)
APOE result shared with family	42/68 (61.8)
Treatment decision changed by biomarker result, n (%)	82 (36.6)
Patient enrolled in research study post-biomarker, n	32
Estimated cost per patient tested, INR	8,800
Cost per case of diagnostic reclassification, INR	28,900

4. Discussion

Across 224 patients undergoing CSF biomarker testing for cognitive symptoms with 4-year follow-up, three observations have direct practical implications. First, the ATN profile distribution in this South Asian tertiary memory clinic is broadly consistent with Western experience, with A+ amyloid profiles in 57% of patients and A+T+ Alzheimer biomarker profile in 43%. The implication is that the biological prevalence of Alzheimer pathology in symptomatic patients attending a memory clinic in this setting matches international experience, supporting routine deployment of biomarker testing rather than treating these results as a characteristically Western phenomenon. Second, the diagnostic reclassification rate of 30.4% approaching one in three patients receiving a biomarker-supported change in diagnostic impression demonstrates the operational value of CSF testing. The two most common reclassifications were (a) MCI patients shifted to prodromal AD with A+ profile (43% of MCI patients), and (b) probable-AD patients with A-T- profile reclassified to non-AD aetiology. Both shifts have substantial clinical implications: the former for prognosis and consideration of disease-modifying therapy, the latter for avoiding inappropriate cholinesterase inhibitor use and seeking alternative diagnoses (Jha, Kumar,, & Neha, 2026; Kumar, Gautam,, & Maitiy, 2026; Bhatnagar, Kumar,, & Shivam, 2026).

Third, the 4-year conversion trajectories provide a biological framework for prognostic counselling. A+T+ MCI patients showed 55% dementia conversion by 4 years, while A-T- MCI patients showed only 17% conversion (and 16% reverted to normal cognition). The implications extend beyond prognostication to treatment decisions: anti-amyloid therapies are only indicated in A+ patients and offer most benefit when started early in the disease course; conversely, A- patients should not receive anti-amyloid therapy and may benefit from evaluation for alternative aetiologies including depression, vascular contribution, or other neurodegenerative pathology (Deepa et al., 2026; Catherine, Gupta, Gopi,, & Swadhi, 2025; Swadhi, Gayathri, Suresh, Catherine,, & Velmurugan, 2025; Vettriselvan, Ramya, et al., 2026).

Implementation considerations include the cost of CSF biomarker testing (approximately INR 8,800 per patient in our setting), the laboratory infrastructure required for batched ELISA testing with appropriate quality control, the training of clinical staff in lumbar puncture technique with acceptably low complication rates, and structured patient counselling about result interpretation and emotional implications. Plasma-based biomarkers (Aβ42/40, phospho-tau-217) are emerging as scalable alternatives to CSF testing and may further reduce barriers to wider deployment (Vijayalakshmi et al., 2025; Vinodh, Subramani,, & Vettriselvan, 2026; Subramani, Chillagattu, et al., 2026; Selvi et al., 2026; Jha, Kumar,, & Neha, 2026; Kumar, Gautam,, & Maitiy, 2026). Genetic counselling for APOE results requires structured infrastructure that many memory clinics still lack. Limitations include the single-centre tertiary setting with patients pre-selected by clinicians considering biomarker testing useful; the 4-year follow-up which captures most early progression but does not address longer-term trajectories particularly in A-T- patients whose progression rate may rise over longer follow-up; the limited APOE coverage (70% of cohort); and the absence of amyloid PET correlation in most patients. The cohort over-represents the cognitively symptomatic population willing to undergo invasive testing and may not reflect the broader community-dwelling cognitively impaired population.

DOI: 10.30726/esij/v13.i3.2026.1330040

ISSN 2394-7187(Online)
ISSN 2394 - 7179 (Print)

5. Conclusion

CSF biomarker testing in this tertiary memory clinic cohort identified an Alzheimer biomarker profile in 57% of symptomatic patients, led to diagnostic reclassification in 30%, and showed 4-year dementia conversion rates ranging from 17% (A-T-) to 55% (A+T+). The biomarker framework provides operationally tractable patient stratification with clear implications for prognostic counselling and treatment decisions, particularly as anti-amyloid therapies move into approved practice. Routine CSF biomarker assessment should be considered for any patient with MCI or atypical dementia presentation where the diagnostic framework would meaningfully inform management.

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DOI: 10.30726/esij/v13.i3.2026.1330040