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RESEARCH ARTICLE

Diagnostic value of fluid-based non-amyloid biomarkers for Alzheimer's disease and related dementias in a clinic-based cohort from South Asia

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Abstract

INTRODUCTION: The rising dementia burden and limited knowledge of fluid biomarkers in South Asians highlights this study's aim on evaluating their utility for the diagnosis of Alzheimer's disease and related dementias (ADRD).

METHODS: Participants with ADRD were recruited from a cognitive disorders clinic in India. We performed cognitive assessments and severity evaluations using standard tests. Serum and cerebrospinal fluid (CSF) levels of glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), total tau, and ubiquitin C-terminal hydrolase L1 (UCHL1) were quantified using a Simoa HD analyzer.

RESULTS: Among the 101 participants, serum GFAP and NfL levels were significantly greater in dementia participants ($n = 70$) than controls. Serum biomarkers significantly correlated with their corresponding CSF levels. Significant correlations were noted for serum and CSF GFAP and NfL in Alzheimer's disease ($\rho = 0.492, 0.664$) and between serum and CSF NfL in frontotemporal dementia ($\rho = 0.727$). Serum GFAP, NfL, and UCHL1 demonstrated high diagnostic accuracy (area under the curve = 0.765–0.806).

DISCUSSION: Our results emphasize the role of fluid biomarkers in diagnosing dementia in low-resource settings in South Asians.

KEYWORDS
Alzheimer's disease, frontotemporal dementia, glial fibrillary acidic protein, neurofilament light chain, serum biomarkers

Highlights

- Serum glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL) levels were significantly greater in patients with dementia than in healthy controls.
- Significant correlation was observed between the serum and cerebrospinal fluid levels of GFAP, NfL, and total tau independent of the baseline demographics or co-morbidities, indicating their potential role in clinical practice.

- Serum biomarker levels were related to the severity of dementia.
- This is one of few studies on fluid-based biomarkers in diverse cohorts with Alzheimer's disease and related dementias in the South Asian cohort with limited resources.

1 | BACKGROUND

Recently, there has been a paradigm shift in the diagnosis of Alzheimer's disease (AD) and related dementias (ADRD) from clinical to biomarker-based diagnosis.[1] This integration of biomarkers along with clinical assessment has improved the diagnostic accuracy and enabled early detection for intervention strategies for individuals at risk of AD progression from mild cognitive impairment (MCI). Central to AD pathogenesis is the amyloid cascade hypothesis, highlighting amyloid beta (Aβ) protein—Aβ42 and Aβ40—as the key pathological hallmarks.[2] While biomarkers like cerebrospinal fluid (CSF) Aβ42/40 and amyloid imaging have been validated for AD diagnosis and disease progression, they are costly, less accessible, invasive, and have limited potential for scalability in large, diverse populations.[3] Blood-based biomarkers such as Aβ42/40 have emerged as promising minimally invasive alternatives, although their diagnostic accuracy remains slightly slower compared to CSF Aβ42/40 despite development of highly sensitive assays.[4]

Over the past decade, ultrasensitive blood assays have identified brain-derived proteins such as neuron-specific cytoskeletal protein neurofilament light chain (NfL)[5] and the glial-derived intermediate filament protein glial fibrillary acidic protein (GFAP).[6] NfL, as a marker of neuroaxonal damage, is strongly associated with frontotemporal dementia (FTD) and shows a robust correlation between CSF and blood.[7,8] Increased GFAP levels reflect astrocyte activation or injury[6] and have demonstrated superior performance over CSF in detecting AD pathology, even in preclinical or MCI stages.[9] These proteins are released into the extracellular space after neuronal or glial injury and are subsequently detectable in the CSF. These assays offer accessible, non-invasive, and cost-effective quantification of the emerging biomarkers, aiding early diagnosis, dementia subtype differentiation, disease monitoring, and treatment response in clinical trials.

In addition, total tau (t-tau) and ubiquitin C-terminal hydrolase L1 (UCHL1) have also been evaluated as markers of neurodegeneration. Tau proteins, located in neuronal axons, stabilize neuronal microtubules, but hyperphosphorylation leads to dissociation and aggregation into insoluble aggregates called neurofibrillary tangles. CSF t-tau can serve as a neuronal injury marker and is increased in many neurodegenerative disorders, such as prion disorders, AD, and FTD.[10] Similarly, UCHL1, a highly abundant cytoplasmic enzyme, modifies the activity of the ubiquitin proteasome system (UPS), which is responsible for the degradation of misfolded proteins. It is found in Aβ plaques and neurofibrillary tangles, supporting evidence that UPS dysfunction may be directly or indirectly involved in the pathogenesis of AD.[11] However, previous studies often lacked representations from diverse populations, limiting the generalizability of findings.

The burden of dementia in South Asia including India is rapidly rising,[12] yet there are limited studies on serum and CSF biomarkers in these diverse contexts. Very little is known about the potential role of these fluid-based biomarkers in low resource settings in India.[13] In addition, clinical implementation of these fluid biomarkers requires an in-depth evaluation of their diagnostic accuracy across the spectrum of ADRD. Furthermore, given the frequent occurrence of mixed brain pathologies and the high burden of vascular risk factors in diverse contexts, such as India, the assessment of biomarker accuracy is required to account for the overlapping comorbidities. With the advancements in disease-modifying therapies for AD,[14] there is an urgent need to develop accessible, non-invasive biomarkers to enable early and accurate diagnosis for AD, and circumvent the need for invasive CSF tests or costly amyloid scans in such resource-limited settings.

The rapid progress in blood-based biomarkers for ADRD contrasts with the limited evidence on fluid-based biomarkers in a diverse, resource-limited setting like South Asia.[15] Our study evaluates diagnostic utility of fluid biomarkers in ADRD for diagnosis, subtype differentiation, and severity prediction before their implementation in specialized clinics. Specifically, the study aims to (1) evaluate the diagnostic performance of serum and CSF biomarkers (NfL, GFAP, t-tau, and UCHL1) in patients with AD or FTD and healthy controls and (2) determine the cutoff and relationship between serum and CSF values for each biomarker in a South Asian low-resource setting, addressing the need for accessible diagnostic tools.

2 | METHODS

2.1 | Participant recruitment and data

This was a prospective study conducted in the Cognitive Disorders Clinic (CDC) of the Department of Neurology and Neurochemistry, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, the largest tertiary institute to which patients are referred from across the country. The CDC provides multidisciplinary care to all patients with neurodegenerative dementias.[16] Participants are assessed by experienced cognitive neurologists and undergo a detailed clinical history, neuropsychological assessment, and brain imaging. Patients with AD and FTD who were diagnosed using standardized diagnostic criteria[17,18] were consecutively recruited for the study. Age- and sex-matched healthy controls with no history or complaint of memory disturbance, behavioral abnormality, or other significant

medical or neurological illness were also included. Participants with reversible or metabolic causes of dementia, such as hypothyroidism; nutritional deficiency; or other dementias, such as Lewy body dementia or Creutzfeldt–Jacob disease; or with significant medical comorbidities that are known to interfere with biomarker assays, such as chronic kidney or liver disease, were excluded.

2.2 | Cognitive assessments

Cognitive evaluation was performed using Addenbrooke's Cognitive Examination (ACE)-III, which is standardized across Indian languages.[19] It evaluates five domains of cognition (attention, memory, fluency, language, and visuospatial abilities) and is used as a measure of global cognitive functioning with a maximum score of 100. The Clinical Dementia Rating (CDR) scale was used to determine the severity of dementia,[20] and behavioral assessment was performed using the Neuropsychiatric Inventory (NPI) in all the participants with dementia.

2.3 | CSF and blood biomarker measures

All biomarker analyses were performed on a single-molecule array (Simoa) HD-X analyzer platform (Quanterix, USA) using Neurology-4-plex-A advantage kits to quantify NfL, GFAP, t-tau, and UCHL1 in serum and CSF samples, according to the manufacturer's instructions. Calibrators were run in triplicate, while samples were analyzed in duplicate at dilutions of 1:4 for serum and 1:100 for CSF. More procedural details are mentioned in the supporting information (see Table S1).

2.4 | Neuroimaging

Structural brain images were acquired using 3T magnetic resonance imaging scanners with T1-weighted scans used to quantify global and focal brain atrophy using different visual rating scales.[21–23] Subcortical white matter hyperintensities (WMHs) suggestive of small vessel disease was defined using the Fazekas scale.[24]

2.5 | Statistical analyses

Data were checked for normality of distribution using the Kolmogorov–Smirnov test. Based on the distribution patterns, parametric and non-parametric tests were used as appropriate. Continuous data are expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR). Categorical data are presented as frequencies and percentages.

Statistical analyses included *t* tests (independent samples *t* tests) for continuous means, chi-squared tests for categorial variables, Mann–Whitney *U* and median tests for non-parametric data. Area under the curve (AUC) from receiver operating characteristic (ROC) analysis was used to determine optimum cutoff values determined based on the Youden index. Pearson and Spearman correlations were used for normally and non-normally distributed data. To correct for multiple comparisons, we applied the false discovery rate (FDR) correction using the Benjamini–Hochberg procedure. All statistical tests were two-tailed, and P values < 0.05 were considered significant. Analyses were conducted using SPSS software version 28, R software version 4.3.1, and GraphPad Prism version 8.0.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using traditional sources (PubMed) as well as preprint literature on fluid biomarkers for Alzheimer's disease and related dementias (ADRD) in South Asia, highlighting limited representation from this region despite global studies focused on Western cohorts. Unique genetic, environmental, and cultural contexts influencing dementia risk in South Asians remain underexplored. Expanding research and developing adaptable diagnostic cut-offs addressing comorbidities in diverse contexts will enhance ADRD diagnosis and advance global understanding.
2. **Interpretation**: Our findings, based on 101 participants within a clinic-based cohort in South India, revealed significantly higher serum glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), and ubiquitin C-terminal hydrolase L1 levels compared to controls, even after accounting for comorbidities. Serum biomarkers correlated strongly with cerebrospinal fluid (CSF) biomarkers and clinical severity, with NfL demonstrating consistent associations. Significant correlations were observed for serum and CSF GFAP and NfL in Alzheimer's disease, and between serum and CSF NfL in frontotemporal dementia.
3. **Future Directions**: Future research should aim to validate emerging blood biomarkers across diverse populations to establish reliable diagnostic thresholds, ensuring their applicability and integration into routine clinical practice for ADRD diagnosis.

3 | RESULTS

3.1 | Sociodemographic characteristics of the cohort

Of the 101 participants included in the study, 72 (71.2%) had dementia, and 29 (28.7%) were healthy controls. The participants in the dementia group were older (61.26 ± 10.31, range 40–84 years) than the controls (55.69 ± 8.97, range 45–72 years). The cohort consisted of 56.94% men in the dementia group and 51.72% in the healthy control group. There

were no significant sex differences between the dementia and healthy control groups. Additionally, no significant differences were found in sex, mean ACE-III score, CDR, or comorbidities between AD and FTD subtypes.

3.2 | Biomarkers in dementia and healthy controls

Compared to the healthy control group, the dementia group had higher median serum GFAP levels (245.0 pg/mL [IQR: 154.5–399.8] vs. 124.0 pg/mL [IQR: 97.7-194.5], $P < 0.001$). Similarly, median serum NfL levels were elevated in dementia patients (60.4 pg/mL [IQR: 40.5–94.3] vs. 21.7 pg/mL [IQR: 16.2–27.8], $P < 0.001$). Median serum UCHL1 levels were also significantly higher in patients with dementia (33.4 pg/mL [IQR: 21.0–54.8] vs. 10.1 pg/mL [IQR: 8.0–19.6], $P < 0.001$; Table 1).

3.3 | Differences in fluid biomarkers between dementia subtypes (AD and FTD)

Participants with dementia were further categorized into AD ($n = 28$) and FTD ($n = 42$) groups, and both serum and CSF samples were available for this group. Only serum biomarkers were available for healthy controls. One serum sample each from the AD and FTD groups showed an error in the analysis, and was excluded. CSF samples were available for 17 patients with AD and 13 patients with FTD.

Among the CSF biomarkers UCHL1 levels were significantly higher in patients with AD (2234.0 pg/mL [IQR: 1795.0–3646.0]) compared to FTD (1271.5 pg/mL [IQR: 1157.0–2479.3], $P = 0.016$). There were no significant differences in CSF biomarker levels of GFAP, NfL, and t-tau between patients with AD and FTD. For the other biomarkers, no significant differences were found between patients with AD and FTD in serum GFAP, NfL, t-tau, and UCHL (Table 1). However, after FDR correction, the difference in CSF UCHL1 between AD and FTD did not remain significant.

No significant sex differences were observed in serum and CSF biomarkers among patients with dementia.

3.4 | Correlation between paired serum and CSF biomarkers

Among the dementia subtypes, a subset of patients with AD ($n = 16$) and FTD ($n = 12$) had both serum and CSF samples. Significant correlations were found between the CSF and serum levels for several biomarkers. Specifically, CSF GFAP correlated significantly with serum GFAP ($r = 0.402$, $P = 0.034$), serum NfL ($r = 0.396$, $P = 0.041$), and serum tau ($r = 0.423$, $P = 0.025$). Additionally, CSF NfL showed a significant correlation with serum NfL ($r = 0.617$, $P = 0.001$). Furthermore, CSF tau was significantly correlated with serum tau ($r = 0.477$, $P = 0.010$), and CSF UCHL1 significantly correlated with serum tau ($r = 0.520$, $P = 0.005$). Among the dementia subtypes, paired serum–CSF biomarker correlations in AD were significant for GFAP ($r = 0.492$, $P = 0.050$) and NfL ($r = 0.664$, $P = 0.007$), while for FTD, this paired serum–CSF correlation was significant for only NfL ($r = 0.727$, $P = 0.007$; Figure 1, Table 2).

Sex-specific variations revealed more consistent correlations between serum and CSF biomarkers in males compared to females. In males, significant correlations were observed between CSF and serum GFAP and NfL, as well as between CSF and serum tau. In contrast, females showed a strong correlation only between CSF and serum NfL ($r = 0.991$, $P < 0.001$; Table 2).

3.5 | Biomarker levels and dementia severity

Significant correlations were observed between CDR-based disease severity and serum levels of GFAP ($r = 0.424$, $P < 0.001$), NfL ($r = 0.393$, $P = 0.001$), and tau ($r = 0.238$, $P = 0.047$). However, no significant correlation was found between CDR-based disease severity and CSF biomarker levels of GFAP ($r = 0.350$, $P = 0.058$), NfL ($r = 0.353$, $P = 0.056$), tau ($r = 0.088$, $P = 0.642$), or UCHL1 ($r = 0.217$, $P = 0.250$).

For the ACE-III scores, there were significant negative correlations observed with serum GFAP ($r = -0.405$, $P = 0.001$) and serum NfL ($r = -0.306$, $P = 0.013$). However, no significant correlations were found between ACE-III scores and CSF biomarkers (GFAP, NfL, tau, UCHL1) or between ACE-III scores and serum tau or UCHL1 levels (Figure 2, Table S3 in supporting information).

3.6 | Serum and CSF biomarkers by neuroimaging parameters

In CSF, significant correlations were observed with NfL in the bilateral entorhinal cortex (ERC), bilateral perirhinal cortex (PRC), left middle temporal (MT), and white matter lesions. The global cortical atrophy score also had a significant correlation with NfL. In serum, significant correlations were found with NfL in the left insula, left anterior temporal, right MT, left MT, bilateral ERC, bilateral PRC, diencephalic region, and the global cortical atrophy score. Additionally, the left Koedam grade had a significant correlation with NfL and the left MT showed a significant correlation with tau (supporting information and Table S4).

3.7 | Diagnostic accuracy of serum and CSF biomarkers

The diagnostic accuracy of CSF and serum biomarkers for discriminating between patients and controls and among patients with different dementia subtypes was tested using ROC curve analysis without any adjustment. In the discrimination between healthy controls and patients with dementia, the ROC curve (Figure 3A) demonstrated high accuracy for serum GFAP, NfL, and UCHL1, with AUC values ranging from 0.765 (GFAP) to 0.865 (NfL) to 0.806 (UCHL1). All the biomarkers showed a minimum positive predictive value of 0.87 but largely varying negative predictive values (min 0.34 for tau and 0.82 for NfL). Across

TABLE 1 Comparison of serum and CSF biomarker characteristics among patients with Alzheimer's disease, frontotemporal dementia, and healthy controls.

Variables	Dementia ($n = 72$)	Healthy controls ($n = 29$)	p value	AD ($n = 29$)	FTD ($n = 43$)	p value
Age, in years (±SD)	62.3 (10.3)	55.69 (8.9)	0.012	62.34 (12.01)	60.53 (9.06)	0.034
Sex, male (%)	41 (56.9)	15 (51.72%)	0.633	14 (48.27%)	27 (62.79%)	0.426
ACE-III (±SD)	46.5 (26.9)	-	-	50.07 (23.70)	43.95 (28.96)	0.360
CDR						
Very mild (%)	23 (22.8)	-	-	10 (34.48%)	13 (30.23%)	0.665
Mild (%)	17 (16.8)	-	-	5(17.24%)	12 (27.90%)	
Moderate (%)	16 (15.8)	-	-	6 (20.68%)	10 (23.26%)	
Severe (%)	16 (15.8)	-	-	8 (27.58%)	8 (18.60%)	
Comorbidities (%)						
Diabetes mellitus	20 (27.8)	0	-	9 (31.0)	11 (25.6)	0.612
Hypertension	24 (33.3)	0	-	13 (44.8)	11 (25.6)	0.091
Cardiac disease	6 (8.3)	0	-	4 (13.8)	2 (4.7)	0.286
Cerebrovascular disease	2 (2.8)	0	-	1 (3.4)	1 (2.3)	0.776
Hypothyroidism	8 (11.1)	0	-	4 (13.8)	4 (9.3)	0.552
Biomarkers						
Serum GFAP Median (IQR)	245.0 (154.5–399.8)	124.0 (97.7-194.5)	<0.001* (<0.001)***	291.0 (130.0-520.0)	240.5 (144.8–381.3)	0.090 (<0.360)***
Serum NfL, pg/mL Median (IQR)	60.4 (40.5–94.3)	21.7 (16.2-27.8)	<0.001* (<0.001)***	55.5 (44.8-77.6)	61.7 (41.7–85.3)	0.134 (<0.402)***
Serum t-tau, pg/mL Median (IQR)	0.99 (0.6–1.5)	0.8 (0.5-1.2)	0.121 (<0.480)***	1.16 (0.7-2.1)	0.93 (0.5–1.6)	0.204 (0.408)***
Serum UCHL1, pg/mL Median (IQR)	33.4 (21.0–54.8)	10.1 (8.0-19.6)	<0.001* (<0.001)***	30.4 (21.7-59.0)	38.6 (16.4–158.0)	0.472 (<0.472)***
**CSF GFAP, pg/mL Median (IQR)	9565.0 (6555.0–14375.0)	-	-	12800.0 (9220.0-14900.0)	6765.0 (4670.0–12345.0)	0.069 (<0.156)***
**CSF NfL, pg/mL Median (IQR)	2375.0 (1437.5–3577.5)	-	-	3280.0 (2260.0-4140.0)	1850.0 (1237.5–4882.5)	0.174 (<0.174)***
**CSF t-tau, pg/mL Median (IQR)	21.4 (13.8–43.4)	-	-	32.7 (13.9-83.2)	15.2 (7.4–32.6)	0.052 (<0.156)***
**CSF UCHL1, pg/mL Median (IQR)	1841.5 (1206.6–3019.0)	-	-	2234.0 (1795.0-3646.0)	1271.5 (1157.0–2479.3)	0.016 (<0.064)***

Abbreviations: ACE-III, Addenbrooke's Cognitive Examination III; AD, Alzheimer's disease; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; FDR, false discovery rate; FTD, frontotemporal dementia; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; SD, standard deviation; t-tau, total tau; UCHL1, ubiquitin C-terminal hydroxylase L1.

The data are shown as the means (SD) or numbers (percentages), or medians with interquartile range (IQR).

*Age = AD > Control ($P = 0.038$) and hence, the comparison among three groups are adjusted for the difference in age; serum GFAP = AD > control ($P = < 0.001$), FTD > control ($P = 0.020$); serum NFL = AD > control ($P = 0.020$), FTD > control (0.001).

**CSF biomarkers were only available for dementia group, AD ($n = 16$) and FTD ($n = 12$).

***Adjusted values (corrected_FDR).

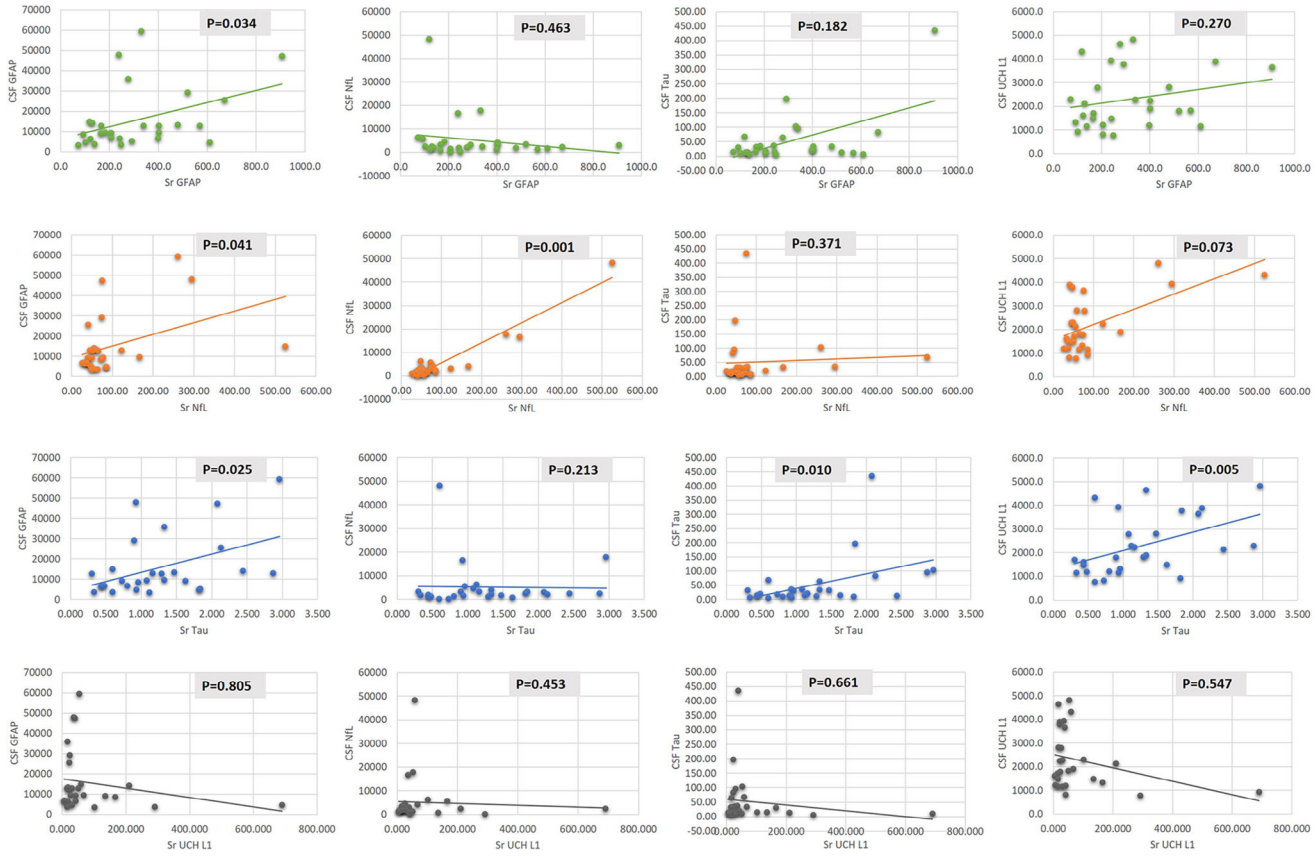

FIGURE 1 Correlations between serum and CSF biomarkers for all participants with dementia. CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; Sr, serum; UCHL1, ubiquitin C-terminal hydroxylase L1

all the reported diagnostic measures, serum NfL levels were consistently elevated. Serum t-tau showed the lowest sensitivity and highest specificity, with a nonsignificant AUC (Table 3 and Figure 3B).

In distinguishing between the dementia groups, only CSF UCHL1 showed greater diagnostic accuracy in distinguishing patients with AD from FTD (cutoff > 1550.5 pg/mL, sensitivity 94.1%, specificity 76.9%, AUC 0.760; Figure 3C). Other serum and CSF biomarkers, including serum GFAP, NfL, t-tau, UCHL1, and CSF GFAP, NfL, and t-tau, did not show significant diagnostic accuracy in differentiating AD from FTD (Figure 4A,B).

4 | DISCUSSION

The current study adds to the growing evidence on the emerging role of serum and CSF biomarkers, including GFAP, NfL, t-tau, and UCHL1, for dementia in a resource-limited setting in an understudied South Asian cohort. We investigated the diagnostic performance of these fluid biomarkers in differentiating healthy controls and dementia subtypes. Serum GFAP and NfL levels were significantly greater in patients with dementia than in healthy controls. There was a significant association between the serum and CSF levels of GFAP, NfL, and t-tau independent of the baseline demographics and co-morbidities. Furthermore, the levels of serum biomarkers were related to the severity of dementia. Based on these findings, our study suggested the use of serum biomarkers, which are less invasive, as a viable alternative to CSF for use as a surrogate for accurate diagnosis in clinical practice. Our study shows utility of serum biomarkers in discriminating participants with dementia and healthy controls in a diverse setting. This will further lead to the development of a biomarker-ready cohort for future clinical trials in a diverse South Asian cohort.

Serum GFAP and NfL were significantly elevated in patients with AD and FTD compared to controls, consistent with prior studies in which these markers were not associated with a specific neuropathologic process but allowed the discrimination between dementia and healthy controls.[25] Although previous studies have shown elevated serum and CSF GFAP levels to be specific for AD[26] and elevated NfL levels for patients with both AD[7,27] and FTD,[28,29] we did not observe such differences in these biomarkers between patients with AD and FTD. In addition, the serum and CSF UCHL1 and t-tau levels did not differ between AD and FTD or between patients with dementia and healthy controls.

Serum and CSF biomarker levels of GFAP, NfL, and t-tau showed significant correlation in dementia patients, especially NfL.[30] In AD, GFAP and NfL correlated strongly between serum and CSF, while in FTD, only NfL showed such correlation. This finding is consistent with previous studies, indicating the diagnostic potential of a combination of biomarkers in differentiating patients with AD, FTD patients,

TABLE 2 Correlations between serum and CSF biomarkers in AD and FTD.

	Correlation (*P* value, 95% CI)			
	Serum			
	GFAP	NfL	Tau	UCHL1
Dementia (*n* = 28)				
CSF				
GFAP	0.402 (0.034)* (0.022–0.68)*	0.396 (0.041)* (0.007–0.681)*	0.423 (0.025)* (0.048–0.694)*	−0.049 (0.805) (−0.424–0.341)
NfL	−0.145 (0.463) (−0.5–0.252)	0.617 (0.001)* (0.299–0.812)*	0.243 (0.213) (−0.154–0.573)	0.148 (0.453) (−0.249–0.502)
Tau	0.260 (0.182) (−0.137–0.585)	0.179 (0.371) (−0.227–0.532)	0.477 (0.010)* (0.115–0.727)*	−0.087 (0.661) (−0.455–0.306)
UCHL1	0.216 (0.270) (−0.182–0.553)	0.350 (0.073) (−0.046–0.651)	0.520 (0.005)* (0.171–0.753)*	−0.119 (0.547) (−0.48–0.277)
AD (*n* = 16)				
GFAP	0.492 (0.053)* (−0.022–0.8)*	0.374 (0.170) (−0.187–0.751)	0.329 (0.214) (−0.215–0.717)	−0.032 (0.905) (−0.531–0.483)
NfL	−0.256 (0.338) (−0.676–0.289)	0.664 (0.007)* (0.215–0.882)*	−0.196 (0.468) (−0.64–0.346)	0.271 (0.311) (−0.275–0.684)
Tau	0.230 (0.392) (−0.315–0.66)	0.096 (0.732) (−0.451–0.591)	0.447 (0.082) (−0.078–0.778)	−0.153 (0.572) (−0.613–0.385)
UCHL1	0.077 (0.778) (−0.449–0.562)	0.307 (0.265) (−0.259–0.716)	0.450 (0.080) (−0.074–0.78)	0.015 (0.957) (−0.497–0.519)
FTD (*n* = 12)				
GFAP	0.098 (0.762) (−0.518–0.648)	0.263 (0.409) (−0.383–0.736)	0.553 (0.062) (−0.049–0.861)	−0.039 (0.905) (−0.611–0.561)
NfL	−0.196 (0.542) (−0.702–0.442)	0.727 (0.007)* (0.245–0.921)*	0.385 (0.217) (−0.261–0.792)	0.042 (0.897) (−0.559–0.614)
Tau	0.154 (0.633) (−0.476–0.679)	0.266 (0.404) (−0.38–0.737)	0.413 (0.183) (−0.23–0.805)	−0.007 (0.983) (−0.591–0.582)
UCHL1	0.112 (0.729) (−0.508–0.656)	0.210 (0.513) (−0.43–0.709)	0.357 (0.255) (−0.291–0.78)	−0.217 (0.499) (−0.713–0.424)

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; t-tau, total tau; UCHL1, ubiquitin C-terminal hydroxylase L1.
*$p < 0.05$.

and healthy controls.[31] Although individual biomarkers could not distinguish AD from FTD, their combined serum–CSF profiles suggest diagnostic value in differentiating dementia subtypes. These correlations between serum and CSF biomarkers in dementia subtypes have clinical implications, indicating that serum could serve as a less invasive surrogate marker for CSF biomarker levels, facilitating wider accessibility to diagnostic assessments. While no significant sex differences were observed in biomarker levels, correlation patterns revealed unexpected variations between males and females. Males showed broader serum–CSF associations across multiple biomarkers, while females showed a robust correlation only for NfL. The evidence on sex differences in these biomarkers remains limited and inconsistent—most studies are based on non-Hispanic White populations and report conflicting results.[32,33] These findings highlight potential sex-related variability in biomarker dynamics, warranting further investigation in larger cohorts.

Consistent with prior literature and our previous study, we found that higher levels of serum biomarkers, including GFAP, NfL, and t-tau, were associated with increasing dementia severity, as determined by the CDR.[34,35] GFAP, a putative marker of astroglial injury, is more highly expressed in the brains of patients with AD than in those of controls.[36] In the serum, GFAP levels have been found to predict cognitive decline early in the disease process. Serum NfL concentration, a marker of axonal damage, has been reported to predict cognitive decline in patients with AD[7] and FTD.[28] Cerebral tau is considered a core biological marker of AD and is closely correlated with cognitive decline.[37] Blood t-tau levels have been associated with multidomain cognitive decline in many cohort studies.[38,39] These findings suggest that serum biomarkers, being less invasive, show promise for tracking disease progression due to their association with disease severity. Increased levels of NfL and GFAP in serum, indicating axonal loss and neuroinflammation respectively, correlated with increased cognitive

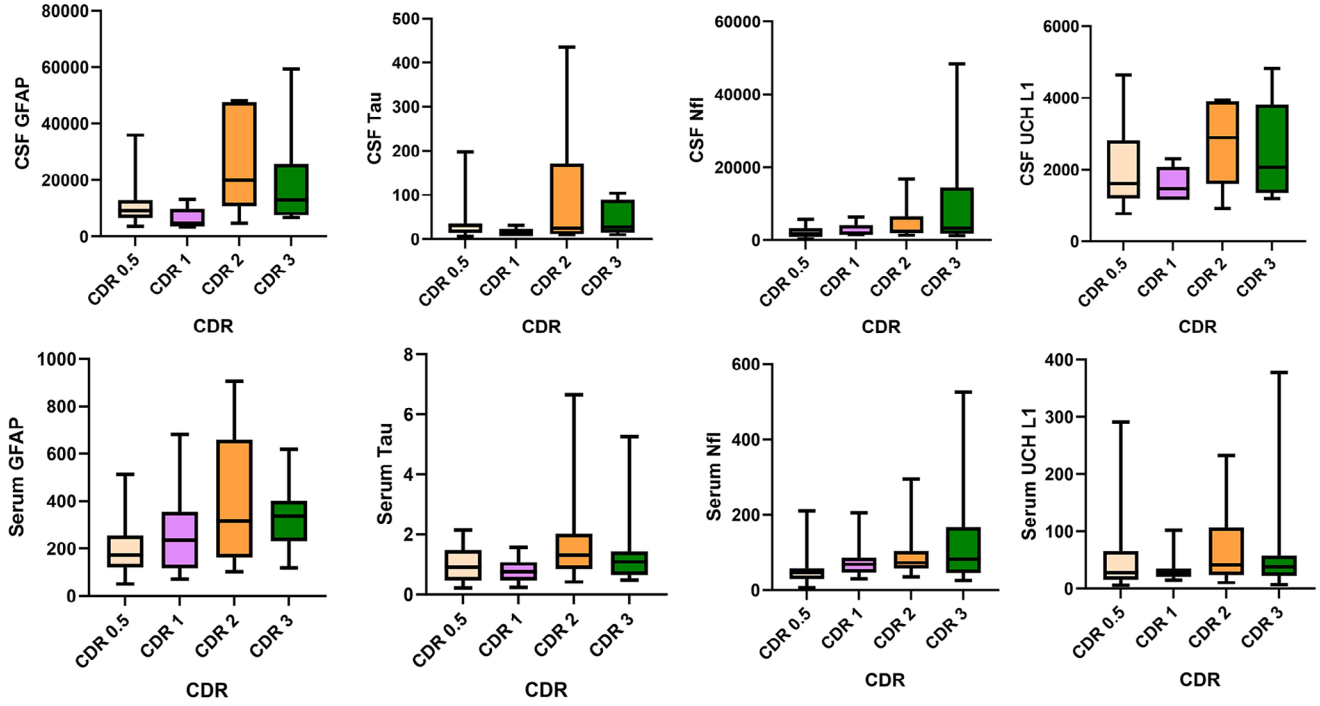

FIGURE 2 Serum and CSF biomarkers by severity of dementia measured by the CDR scale. CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; UCHL1, ubiquitin C-terminal hydroxylase L1

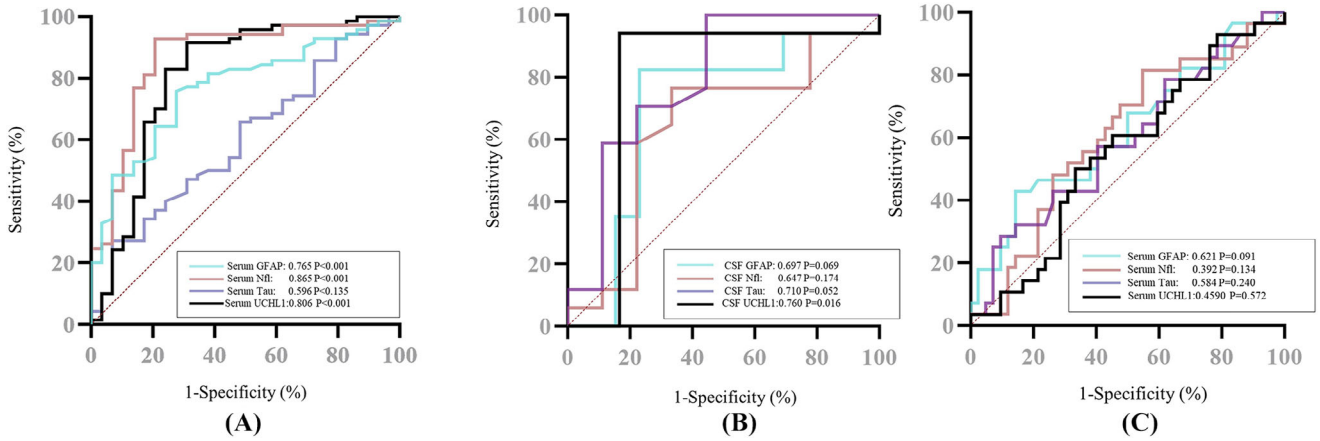

FIGURE 3 Accuracy of serum and CSF biomarkers in detecting AD, FTD, and healthy controls; (A) ROC for serum biomarkers between cases and controls, (B) ROC for serum biomarkers between AD and FTD, (C) ROC for CSF biomarkers between AD and FTD. AD, Alzheimer's disease; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; ROC, receiver operating characteristic; UCHL1, ubiquitin C-terminal hydroxylase L1

impairment, as observed in previous studies.[7,31] This had a stronger effect in serum than CSF, further strengthening the evidence that serum NfL and GFAP can be used as accurate and less invasive biomarkers than CSF NfL and GFAP. In addition, our findings of significant associations between serum and CSF NfL, and brain imaging markers of brain atrophy and WMH are corroborated by previous studies.[7,28]

Replication of similar findings with newer serum biomarkers across diverse cohorts supports their use as clinical trial endpoints or a marker for the progression of AD and related neurodegenerative dementias, though larger sample size is needed to further understand the longitudinal relationship between changes in the levels of these biomarkers and cognitive outcomes.

With regard to diagnostic accuracy, except for serum t-tau, all other biomarkers, including serum GFAP, NfL, and UCHL1, showed significant diagnostic efficacy in discriminating patients with dementia from healthy controls. CSF UCHL1 outperformed all other serum and CSF

TABLE 3 Sensitivity, specificity, and positive and negative predictive values of serum and CSF biomarkers for differentiating patients with dementia from controls and subtypes of dementia.

Discrimination	Markers	AUC (*P* value)	Youden index (cut-off value)	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Between dementia and controls	S GFAP	0.765 (<0.001)	0.478 (154)	75.4%	72.4%	0.87	0.55	75.5%
	S NfL	0.865 (<0.001)	0.721 (28.45)	92.8%	79.3%	0.92	0.82	92.6%
	S Tau	0.596 (0.135)	0.177 (1.48)	24.6%	93.1%	0.91	0.34	28.6%
	S UCHL1	0.806 (<0.001)	0.310 (14.41)	91.3%	69%	0.88	0.76	90.7%
Between dementia subtypes AD and FTD	S GFAP	0.621 (0.091)	0.302 (398.5)	44.4%	85.7%	0.71	0.87	51.7%
	S NfL	0.392 (0.134)	0.082 (29.7)	96.3%	11.9%	0.63	0.81	75.1%
	S Tau	0.584 (0.240)	0.201 (1.83)	29.6%	90.5%	0.52	1.00	42.4%
	S UCHL1	0.459 (0.572)	0.101 (21.3)	81.5%	28.6%	0.73	0.95	63.1%
	CSF GFAP	0.697 (0.069)	0.593 (9215)	82.4%	76.9%	0.67	0.69	83.3%
	CSF NfL	0.647 (0.174)	0.457 (2015)	76.5%	69.2%	0.62	0.69	77.3%
	CSF Tau	0.710 (0.052)	0.357 (31.35)	58.8%	76.9%	0.67	0.65	58.2%
	CSF UCHL1	0.760 (0.016)	0.710 (1550.5)	94.1%	76.9%	0.47	0.69	93.5%

Abbreviations: AD, Alzheimer's disease; AUC, area under the curve; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; NPV, negative predictive value; PPV, positive predictive value; t-tau, total tau; UCHL1, ubiquitin C-terminal hydroxylase L1.

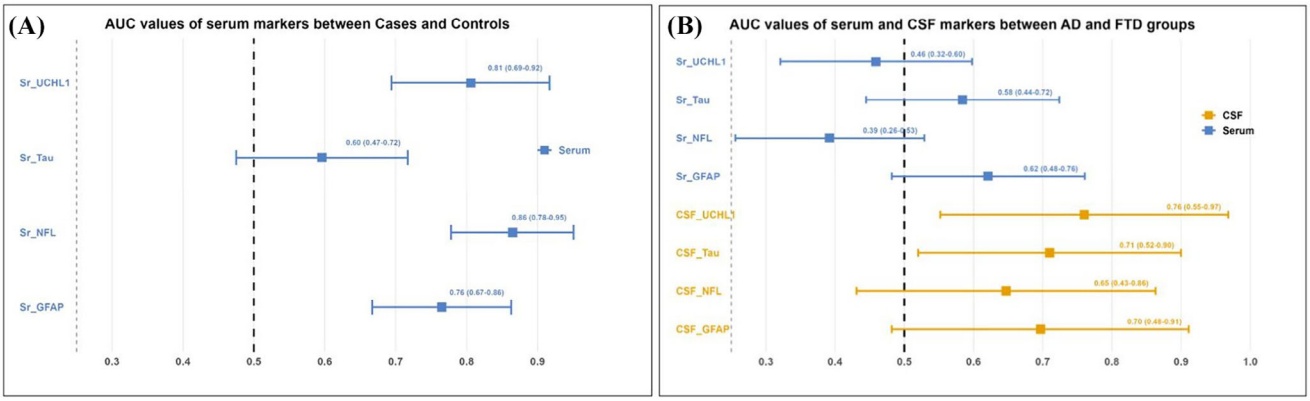

FIGURE 4 A, Forest plot showing the diagnostic performance of serum biomarkers based on AUC values between patients with dementia and controls; (B) forest plot showing the diagnostic performance of serum and CSF biomarkers based on AUC values between patients AD and FTD. AUC, area under the curve; AD, Alzheimer's disease; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; ROC, receiver operating characteristic; UCHL1, ubiquitin C-terminal hydroxylase L1

biomarkers in differentiating AD from FTD, with ROC analysis showing a specificity of 76.9%, sensitivity of 94.1%, and diagnostic efficacy (AUC = 0.760). This finding is in agreement with previous studies that reported good diagnostic performance of UCHL1 in differentiating AD patients from non-AD patients.[11] Increased CSF levels of UCHL1 have been linked to neuronal loss and traumatic brain injury.[40] This association with neurodegeneration is supported by the strong positive correlation between UCHL1 levels and t-tau levels observed in our cohort. However, no difference in UCHL1 levels was detected between patients with FTD and healthy controls, consistent with previous studies.[41] Further, after correcting for multiple comparisons, the adjusted values of difference in CSF UCHL1 between AD and FTD was no longer statistically significant. Our findings are preliminary and exploratory, and larger cohorts are warranted for validating these findings.

While the biomarkers hold promise for early and accurate diagnosis, and monitoring of neurodegenerative dementias, there is paucity of literature on how comorbidities influence these biomarkers, particularly in diverse and resource-limited settings. Most studies conducted to date have been from high-income countries with predominantly non-Hispanic cohorts limiting generalizability. Given the high prevalence of chronic conditions like hypertension, diabetes, cardiovascular disease, hypothyroidism, and cerebrovascular disease in aging populations, it is critical to understand the effect of these comorbidities

on biomarker levels—either independently or in combination. For instance, hypertension-related cardiovascular disease has been associated with higher levels of serum NfL, which may be attributed to microvascular brain injury.[42,43] Similarly, diabetes, impaired kidney function, and obesity can influence NfL and GFAP levels in the blood.[42,44,45] There is emerging evidence to suggest that biomarkers such as UCHL1 and t-tau are also affected by comorbidities such as hypertension, cardiovascular diseases,[46] and hepatorenal dysfunction.[47] These studies underscore the need to account for comorbidities when interpreting biomarker data as these influences may confound dementia diagnosis. There is a critical need for large, well-powered, multi-ethnic studies to unravel these complex interactions and enhance the precision of biomarker-based diagnosis.

The strengths of the study were the use of the Simoa neurology 4-plex-A assay to assess all biomarkers in a common sample set and the use of an assay matrix to ensure that pre-analytic variables and inter-assay variability did not influence the results of the comparative study. When interpreting the observations of our study, it should be noted that the study was a cross-sectional, single-center study with a relatively small sample size and non-normal distribution of several variables not allowing us to perform in-depth analysis. Participants with MCI, which would have allowed evaluation of these biomarkers at an earlier disease stage, were not included in the study, and will need to be included in future studies. Another limitation of the study was that the diagnostic groups were based on clinical criteria due to non-availability of a gold standard to determine diagnostic accuracy. In addition, the healthy control group was relatively small and their cognitive assessments were not available. Nevertheless, this is one of the few studies on blood and CSF biomarkers in patients with dementia in the Indian context with limited resources. Our study demonstrates feasibility to conduct biomarker evaluation in our understudied populations with vascular comorbidities and findings can contribute to understanding of the influence of comorbidities on these biomarkers. Our study also paves the way for establishing the role of newer biomarkers such as phosphorylated tau217[48] in diagnosis of dementias in a diverse context. Future longitudinal multicentric studies in larger diverse cohorts are needed for developing harmonized global study cohorts to ensure clinical trial readiness in the underrepresented populations.[49]

5 | CONCLUSIONS

Our study confirms the feasibility of performing biomarker analysis in a low-resource South Asian setting. Serum and CSF biomarker levels demonstrated efficacy in discriminating between dementia and healthy controls, and between dementia subtypes, with strong serum–CSF correlation indicating serum as a less invasive alternative. The results of the study bring an essential step forward for validating and implementing blood biomarkers on a large scale. However, further longitudinal studies in diverse cohorts with novel emerging biomarkers are required for validation and establishing diagnostic cut-off values before clinical implementation of blood biomarkers for routine clinical use for neurodegenerative dementias.

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CONFLICT OF INTEREST STATEMENT

The authors report no competing interests to declare. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

The online version contains the supplementary data. Raw data are available upon reasonable request to the corresponding author

CONSENT STATEMENT

The study was performed in compliance with the guidelines of human experimentation and the protocol was approved by the institute's ethics committee (NIMH/DO/IEC (BS & NS DIV)/2020). We obtained written informed consent from all the participants and procedures were done in accord with the Declaration of Helsinki.

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