Title

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Journal

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 17(1)

ISSN

2352-8729

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Publication Date

2025

DOI

10.1002/dad2.70078

Peer reviewed

Received: 22 November 2024 | Accepted: 23 November 2024

DOI: 10.1002/dad2.70078

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Clinical and neuropathological associations of plasma $A\beta_{42}/A\beta_{40}$, p-tau217 and neurofilament light in sporadic frontotemporal dementia spectrum disorders

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Abstract

INTRODUCTION: Plasma amyloid beta$_{42}$/amyloid beta$_{40}$ ($A\beta_{42}/A\beta_{40}$) and phosphorylated tau217 (p-tau217) identify individuals with primary Alzheimer's disease (AD). They may detect AD co-pathology in the setting of other primary neurodegenerative diseases, but this has not been systematically studied.

METHODS: We compared the clinical, neuroimaging, and neuropathological associations of plasma $A\beta_{42}/A\beta_{40}$ (mass spectrometry), p-tau217 (electrochemiluminescence), and neurofilament light ([NfL], single molecule array [Simoa]), as markers of AD co-pathology, in a sporadic frontotemporal dementia (FTD) cohort ($n = 620$).

RESULTS: $A\beta_{42}/A\beta_{40}$ showed no clinicopathological associations. High p-tau217 was present in amnestic dementia (AmD) presumed to be due to FTD, logopenic primary progressive aphasia (lvPPA), and *APOEε4* carriers, and correlated with worse baseline and longitudinal clinical scores, lower hippocampal volumes, and more severe AD co-pathology (Braak Stage). NfL was elevated in all FTD phenotypes, and correlated with clinical scores and frontotemporal brain volumes.

DISCUSSION: Plasma p-tau217 has clinical, neuroimaging, and neuropathological correlates in sporadic FTD and may identify FTD cases with AD co-pathology.

KEYWORDS
Alzheimer's disease, fluid biomarkers, frontotemporal dementia, plasma amyloid, plasma neurofilament, plasma tau

Funding information
NINDS; John Douglas French Alzheimer's Foundation; NIA

Highlights

- Alzheimer's disease (AD) features could be identified with plasma phosphorylated tau217 (p-tau217) in frontotemporal lobar degeneration (FTLD).
- Plasma p-tau217 is a better discriminator of AD co-pathology and AD-associated features in FTLD than plasma amyloid beta$_{42}$/amyloid beta$_{40}$ (Aβ_{42}/Aβ_{40}) and neurofilament light (NfL).
- In FTLD, plasma p-tau217, but not Aβ_{42}/Aβ_{40} or neurofilament light, has phenotypical, neurocognitive, and neuroimaging correlates suggestive of AD co-pathology.

1 | BACKGROUND

Emerging plasma biomarkers are improving the diagnostic approach to Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD). Plasma amyloid beta$_{42}$/amyloid beta$_{40}$ (Aβ_{42}/Aβ_{40}) and phosphorylated tau217 (p-tau217) have excellent performance in discriminating patients with neuropathology-confirmed AD from cognitively-healthy controls or other neurodegenerative diseases.[1–3] Both biomarkers identify patients with positive amyloid or tau positron emission tomography (PET) in symptomatic, prodromal and even presymptomatic AD stages, and correlate with cognitive function and rates of clinical progression.[4–6] Plasma Aβ_{42}/Aβ_{40} and p-tau181 tend to normalize their concentrations in response to the therapeutic effects of anti-amyloid immunotherapies, and they are gaining a central role as screening tools and exploratory outcome measures in clinical trials of AD.[7,8] Neurofilament light (NfL) chain is a nonspecific, but highly sensitive marker of neurodegeneration that discriminates patients with FTLD from other neurodegenerative conditions, and has been introduced to clinical practice for this purpose.[9] NfL predicts clinical progression in both AD and FTLD, and is being used as an outcome measure in clinical trials of AD and FTLD.[8,10–13] FTLD is the pathological substrate of frontotemporal dementia (FTD), a spectrum of aggressive clinical syndromes that feature impairments in behavior, motor function, and cognition.[14]

One emerging question is whether the clinical performance of plasma Aβ_{42}/Aβ_{40}, p-tau217, and NfL is affected in the setting of multiproteinopathy. The importance of this question is that AD and FTLD often coexist, and overlap clinically, making it difficult to distinguish between the two pathologies. Up to 64% cases of autopsy-confirmed primary FTLD have some form of AD co-pathology,[15] and about 17% of patients with behavioral variant FTD (bvFTD) and 23% of corticobasal syndrome (CBS), both classically considered within the FTD spectrum, have primary AD pathology.[16–18] Previous studies have shown that FTD typically features high NfL and normal plasma amyloid and tau biomarkers. Yet, those same studies show large variability of the concentrations of plasma biomarkers in FTD, raising the possibility that these may be detecting the presence of AD co-pathology. Indeed, a subset of patients with FTLD have positive amyloid PET or plasma p-tau217 concentrations that correlate with Thal phase, Braak stage, and neuritic plaque CERAD scores.[3] Nevertheless, a systematic comparison of the performance of Aβ_{42}/Aβ_{40}, p-tau217, and NfL in relation to their clinical associations with scales of disease severity, brain volumes, and neuropathological data in suspected FTLD has not been conducted. Identification of AD co-pathology in FTLD may open new avenues to further care and research for the two conditions. The goal of this study is to compare the clinical performance of plasma Aβ_{42}/Aβ_{40}, p-tau217, and NfL, measured with state-of-the-art ultrasensitive technologies, in a large cohort of sporadic FTD. We contrast their relationships with FTD disease severity; apolipoprotein E (*APOE*) genotype; cognitive, motor, and social function; brain volume; and in a subset of cases with available autopsy data, neuropathological features.

2 | METHODS

2.1 | Study design and participants

This cross-sectional study included 620 participants (46% female, median age 69 ± 4 years) with available data on any of the three plasma biomarkers of interest, and recruited through the multi-site ALLFTD observational project of FTD.[19] In the entire cohort, 1.7% of cases had missing data for Aβ_{42}/Aβ_{40}, 13% for p-tau217, and 8.6% for NfL. Only sporadic cases meeting clinical diagnostic criteria for an FTD syndrome, and cognitively healthy controls were included. Participants were confirmed to be negative for a genetic cause of FTD through research genetic testing.[20] Sporadic phenotypes included mild cognitive or behavioral impairment (MCI), bvFTD, CBS, FTD with amyotrophic lateral sclerosis (FTD/ALS), logopenic primary progressive aphasia (lvPPA), semantic primary progressive aphasia (svPPA), non-fluent variant primary progressive aphasia (nfvPPA), progressive supranuclear palsy-Richardson's syndrome (PSP), amnestic dementia (AmD) and asymptomatic controls in the same families from which patients with affected phenotypes were recruited (CN).[21] MCI included participants with mild amnestic, non-amnestic or behavioral impairment.[22] AmD included cases with an amnestic dementia syndrome, that may or not be due to AD. This was in consideration that some forms of sporadic FTLD, such as FTLD-tau Pick's

disease[23] or FTLD-TDP type A,[24] occasionally have amnestic presentations. Pathology-confirmed cases were co-enrolled in the University of California, San Francisco (UCSF) Brain Bank Program. The study was conducted following the ethical standards of the Declaration of Helsinki, and all participants or surrogate decision-makers provided informed consent for participation. The study protocol was approved by a centralized Institutional Review Board.

2.2 | Biomarker measurement

Plasma samples were collected during the baseline research visit and processed using a standardized protocol described previously.[3] Plasma $A\beta_{42}$ and $A\beta_{40}$ concentrations were measured by immunoprecipitation followed by mass spectrometry.[25] Plasma p-tau217 concentrations were determined by a high-sensitivity electrochemiluminescence immunoassay,[3] and NfL was quantified with Simoa.[26] All assays were performed in a batch-wise manner to minimize variability, and laboratory personnel were blinded to the clinical data.

2.3 | Clinical assessments, *APOE* genotype, and neuroimaging

Clinical variables of interest included FTLD-specific disease severity measured with the Clinical Dementia Rating (CDR) dementia staging instrument plus behavior and language domains from the National Alzheimer's Disease Coordinating Center (NACC) Frontotemporal Lobar Degeneration module sum of boxes (CDR+NACC/FTLDsb).[27] Global cognition was measured with the Montreal Cognitive Assessment (MoCA).[28] Verbal memory was measured with the delayed recall score on the short form of the California Verbal Learning Test, second edition (CVLT-I).[29] Motor function was measured with the Unified Parkinson's Disease Rating Scale, motor component (UPDRS III).[30] Social cognition was measured with the Revised Self-Monitoring Scale (RSMS).[31] Research genetic testing for *APOE* was conducted in a centralized laboratory as described previously.[32] Brain volumetric measures (n = 137 cases) were obtained from 1.5T or 3T structural MRI scans (n = 137). Acquisition, processing, and analyses of images were done with a standardized protocol, per the Mayo Clinic's Aging and Dementia Imaging Research Laboratory, as described previously.[33]

2.4 | Neuropathological assessment

Primary neuropathological diagnosis was determined at autopsy in a subset of cases enrolled through the UCSF Brain Bank Program (n = 38). The neuropathological assessments followed previously described protocols.[17] FTLD cases were classified into tau, TDP-43, and FUS molecular classes and their subtypes. AD co-pathology stages were determined using Alzheimer's disease neuropathologic change (ADNC),[34] Braak,[35] and Thal[36] staging systems. ADNC staging assesses $A\beta$ plaques and tau tangles in specific brain regions. Braak staging maps tau pathology progression, detailing neurofibrillary tangle distribution. Thal staging focuses on $A\beta$ plaque distribution, categorizing deposition severity.

RESEARCH IN CONTEXT

1. **Systemic review**: AD and FTLD overlap clinically and co-exist as neuropathological entities. Plasma $A\beta_{42}/A\beta_{40}$, p-tau217, and NfL are markers of neurodegeneration that discriminate between AD and FTLD. There are no systematic comparisons of the performance of these three biomarkers in relation to their associations with clinical disease severity, brain volumes assessed by neuroimaging, and neuropathological features in sporadic FTLD cohorts.
2. **Interpretation**: High plasma p-tau217, but not $A\beta_{42}/A\beta_{40}$ or NfL, was related to more severe Braak scores, *APOEε4* carriership, amnestic and logopenic aphasia phenotypes, worse memory function, and lower hippocampal volumes, regardless of the primary FTLD diagnosis.
3. **Future directions**: Plasma p-tau217 has meaningful associations with clinical, neuroimaging, and neuropathological features of AD as co-pathology of primary FTLD, and it could be used as a tool to advance FTLD care and research, and for the study of the multi-proteinopathy characteristic of sporadic neurodegenerative diseases.

2.5 | Statistical analyses

Biomarker data were explored visually with box plots. The $A\beta_{42}/A\beta_{40}$ ratio was used to test clinical performance since it is a better marker of amyloidosis compared to individual values of its components.[37] Plasma p-tau217 and NfL concentrations were log transformed for analyses. Comparative analysis of biomarker concentrations by sex was done with t-tests. Biomarker concentration differences across FTD phenotypes, disease severity, *APOE* genotype, and pathological diagnoses were performed with analysis of variance (ANOVA) or general linear models. Biomarker diagnostic performance was assessed with receiver operating characteristic (ROC) curves, and cutoff values were generated with Youden indices.[38] We used a nonparametric approach to compare the areas under two or more ROC curves.[39]

Baseline associations between biomarkers and clinical variables and brain volumes were determined with linear regressions corrected for age and sex. Regressions with brain volumes were additionally corrected for total intracranial volume. Brain MRI regions of interest were selected based on the Desikan–Killiany atlas to form regional composites of left, right, and combined frontal, temporal, parietal, and occipital regions, as described before.[40] Additionally, regions

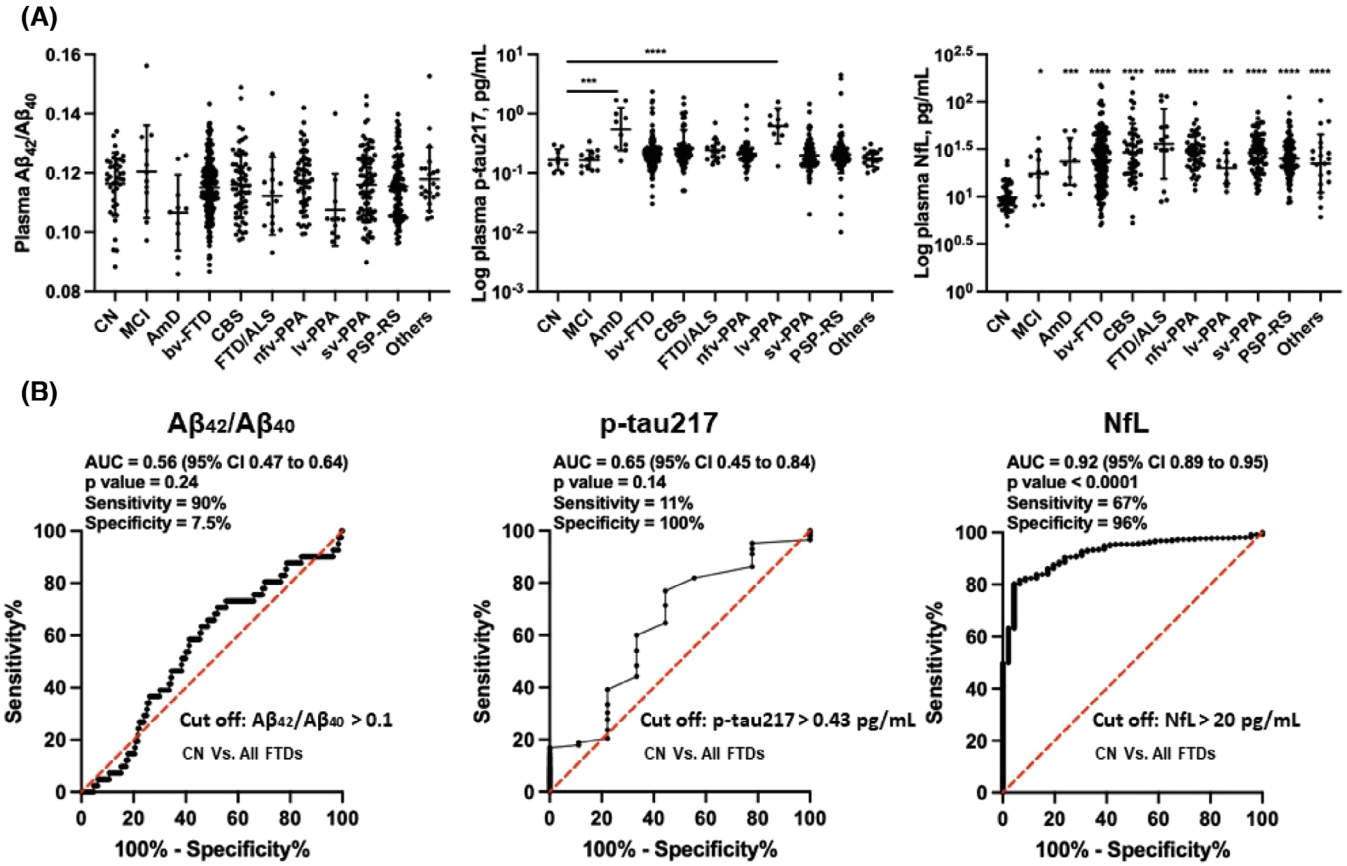

FIGURE 1 Plasma biomarker concentrations by clinical phenotype in frontotemporal dementia spectrum disorders. (A) Plasma $A\beta_{42}/A\beta_{40}$, p-tau217, and NfL concentrations by phenotype. (B) ROC plots of plasma biomarkers for control versus all symptomatic phenotypes. $A\beta_{42}/A\beta_{40}$, amyloid $beta_{42}$/amyloid $beta_{40}$; AmD, amnestic dementia; bvFTD, behavioral variant frontotemporal dementia; CBS, corticobasal syndrome; FTD/ALS, frontotemporal dementia with amyotrophic lateral sclerosis; lvPPA, logopenic primary progressive aphasia; MCI, mild cognitive or behavioral impairment; NfL, neurofilament light chain; svPPA, semantic primary progressive aphasia; nfvPPA, nonfluent primary progressive aphasia; PSP-RS progressive supranuclear palsy-Richardson syndrome; ROC, receiver operating characteristic. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, **** = $p < 0.0001$.

vulnerable in AD were tested separately, including the hippocampus, posterior cingulate cortex, precuneus, angular gyrus, and supramarginal gyrus. Linear mixed-effects models (LMM) tested the relationship of baseline fluid biomarker concentrations with the longitudinal change in clinical scales. Models were corrected for age, sex, and *APOE* genotype and included random slopes and intercepts. We initially evaluated biomarkers as both continuous and categorical independent variables. However, according to the Bayesian information criterion (BIC), employing biomarkers as a categorical variable resulted in a lower BIC and better model fit, and we opted for the categorical biomarker variables. Categorical variables were generated using cutoff values obtained through ROC curves. The ROC curve cutoff values were 0.1 for $A\beta_{42}/A\beta_{40}$, 0.43 pg/mL for p-tau217, and 20 pg/mL for NfL. A two-tailed *p*-value < 0.05 was considered statistically significant. All statistical analyses were performed with R and GraphPad Prism version 10.

3 | RESULTS

3.1 | Plasma biomarker concentrations by sporadic FTD phenotype and *APOE* genotype

Phenotypes did not differ by plasma $A\beta_{42}/A\beta_{40}$ ratios. Plasma p-tau217 concentrations, however, were elevated in AmD (median 0.79 pg/mL ± interquartile range 0.7 pg/mL) and lvPPA (0.65 ± 0.5 pg/mL), compared to other phenotypes (0.2 ± 0.1 pg/mL) or controls (0.15 ± 0.1 pg/mL, $p < 0.001$ and $p < 0.0001$, respectively). In turn, plasma NfL was elevated in all phenotypes, compared to controls (Figure 1 and Table 1). In the whole cohort, *APOEε4* carriers had lower $A\beta_{42}/A\beta_{40}$ and higher p-tau217 compared to non-carriers ($A\beta_{42}/A\beta_{40}$, 0.10 ± 0.01 vs. 0.18 ± 0.01, respectively, $p < 0.0001$; p-tau217, 0.3 ± 0.3 pg/mL vs. 0.19 ± 0.1 pg/mL, respectively, $p < 0.0001$, Figure S1). NfL concentrations did not differ by *APOE* genotype.

TABLE 1 Baseline clinical features of sporadic FTD cohort.

Clinical phenotype	CN	MCI	AmD	bvFTD	lvPPA	nfvPPA	svPPA	FTD/ALS	CBS	PSP	Others
Total number, *n* (%)	47 (7.6)	15 (2.5)	10 (1.6)	183 (29.5)	11 (1.7)	57 (9.2)	82 (13.3)	15 (2.4)	65 (10.4)	110 (17.7)	25 (4.1)
Neuropathological data available, *n* (%)	0	0	1 (10)	11 (6)	0	3 (5)	9 (11)	2 (13)	3 (5)	8 (7)	1 (4)
Volumetric MRI data available, *n* (%)	35 (74)	3 (20)	1 (10)	41 (22)	1 (9)	5 (9)	9 (11)	1 (7)	9 (14)	28 (25)	4 (16)
Sex (female, *n*, %)	35 (75)	8 (53)	2 (20)	69 (38)	6 (55)	31 (54)	42 (51)	4 (27)	26 (40)	52 (47)	9 (36)
Age at visit, years, median (IQR)	64 (9)	70 (12.3)	69 (8)	63 (12)	72 (7)	71 (12)	66 (10)	59 (17)	70 (14.3)	70 (10)	64 (11)
Education, years, median (IQR)	16 (5)	18 (6)	17 (5)	16 (4)	18 (5)	16 (4)	16 (3)	16 (5)	17 (4)	16 (4)	16 (6)
Race (White, *n*, %)	39 (83)	11 (73)	9 (90)	170 (93)	11 (100)	48 (84)	80 (98)	13 (87)	55 (85)	90 (82)	20 (80)
*APOE*ε4 carrier, *n* (%)	3 (6)	4 (27)	4 (40)	37 (20)	7 (64)	10 (18)	22 (27)	4 (27)	15 (23)	21 (19)	1 (4)
APOE ε2/ε2, *n* (%)	0	1 (6.7)	0	0	0	1 (2)	0	0	0	0	0
APOE ε2/ε3, *n* (%)	1 (2)	0	0	20 (11)	0	7 (12)	8 (10)	3 (20)	7 (11)	15 (14)	5 (20)
APOE ε2/ε4, *n* (%)	1 (2)	0	0	2 (1)	0	1 (2)	1 (1)	0	2 (3)	1 (1)	1 (4)
APOE ε3/ε3, *n* (%)	4 (9)	9 (60)	6 (60)	114 (62)	3 (27)	33 (58)	47 (57)	7 (46)	36 (55)	65 (59)	14 (56)
APOE ε3/ε4, *n* (%)	3 (6)	3 (20)	4 (40)	35 (19)	7 (64)	9 (16)	22 (27)	3 (20)	14 (21)	19 (17)	1 (4)
APOE ε4/ε4, *n* (%)	0	1 (6.7)	0	2 (1)	0	1 (2)	0	1 (7)	1 (1)	2 (2)	0
Unknown *APOE*	38 (81)	1 (6.6)	0	10 (6)	1 (9)	5 (8)	4 (5)	1 (7)	5 (8)	8 (7)	4 (16)
FTLD CDR sum of boxes, median (IQR)	0 (0)	3 (1.4)	6.5 (2)	9 (3)	3 (2)	4 (2)	7 (2)	N/A	5 (3)	7.5 (3)	5 (3.5)
MoCA	28 (1)	25 (2)	16 (12)	20 (7)	15 (5)	23 (4)	17 (5)	N/A	24 (5)	22 (4)	23 (8)
UPDRS	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	5 (4)	0 (0)	N/A	23 (11)	28 (9)	5 (3)
RSMS	49 (5)	41 (3)	30 (15)	19 (7)	46 (15)	42 (15)	23 (8)	N/A	40 (14)	32 (9.3)	30 (9)
CVLT late recall	8 (2)	6 (2)	0 (0)	3 (3)	4 (3)	6 (2)	0 (0)	N/A	6 (2.3)	5 (2)	5 (5)
Plasma $A\beta_{42}/A\beta_{40}$, median (IQR)	0.12 (0.01)	0.12 (0.02)	0.1 (0.02)	0.12 (0.01)	0.1 (0.01)	0.12 (0.01)	0.12 (0.02)	0.1 (0.02)	0.12 (0.02)	0.12 (0.02)	0.12 (0.01)
Plasma p-tau217, pg/mL, median (IQR)	0.15 (0.1)	0.18 (0.1)	0.79 (0.7)	0.2 (0.09)	0.65 (0.5)	0.2 (0.08)	0.18 (0.1)	0.23 (0.1)	0.22 (0.1)	0.2 (0.09)	0.17 (0.08)
Plasma NfL, pg/mL, median (IQR)	9.2 (4.7)	17.8 (17)	23.1 (29)	24.1 (26)	21.2 (12)	29 (17)	29.6 (20)	36.3 (41)	28.9 (27)	24.3 (15)	24 (19)

Note: "Others" group includes: alcohol use disorder, amyotrophic lateral sclerosis, Parkinson's disease, unspecified cerebrovascular disease, FOSMN, unspecified language disorder and primary psychiatric disorder.
Abbreviations: $A\beta_{42}/A\beta_{40}$, amyloid beta$_{42}$/amyloid beta40; AmD, amnestic dementia; *APOE*, apolipoprotein E; bvFTD, behavioral variant frontotemporal dementia; CBS, corticobasal syndrome; CDR, Clinical Dementia Rating; CDR+NACC+FTLDsb, CDR Dementia Staging Instrument plus Behavior and Language domains from the National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration module sum of boxes; CN, cognitively normal; CVLT, California Verbal Learning Test; FOSMN, facial-onset sensory motor neuropathy; FTD, frontotemporal dementia; FTD/ALS, frontotemporal dementia with amyotrophic lateral sclerosis; IQR, interquarile range; lvPPA, logopenic primary progressive aphasia; MCI, mild cognitive or behavioral impairment; MoCA, Montreal Cognitive Assessment; nfvPPA, non-fluent variant primary progressive aphasia; PSP, progressive supranuclear palsy-Richardson's syndrome; RSMS, Rating Scale for Social and Moral Sensitivity; svPPA, semantic primary progressive aphasia; UPDRS, Unified Parkinson's Disease Rating Scale.

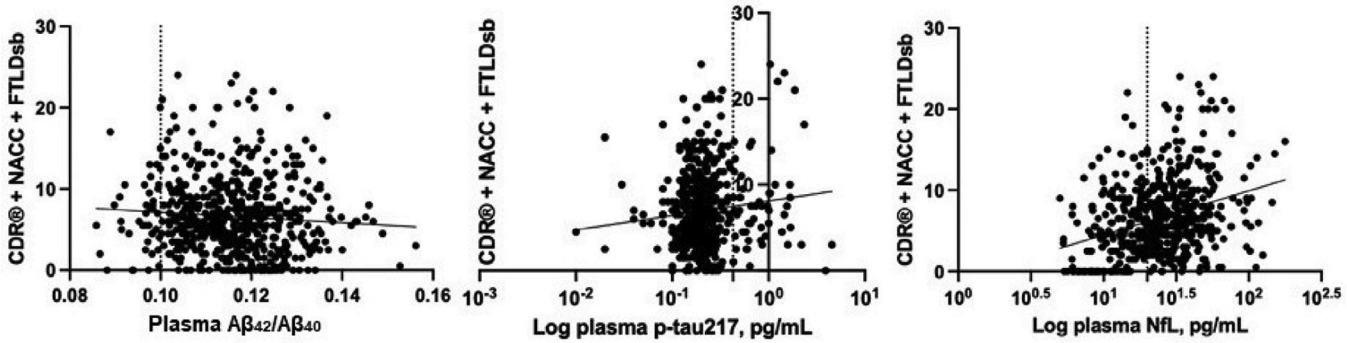

FIGURE 2 Associations between baseline plasma biomarkers and baseline disease severity across the whole cohort. The vertical dotted line represents the cut-point value to discriminate controls from symptomatic patients for each biomarker.

3.2 | Clinical diagnostic performance

Only plasma NfL showed excellent discrimination between controls and any symptomatic FTD (AUC 0.92, 95% confidence interval [CI] 0.89–0.95, $p < 0.0001$, 67% sensitivity, 96% specificity, Figure 1B). In contrast, $A\beta_{42}/A\beta_{40}$ (AUC 0.56, 95% CI 0.47–0.64, $p = 0.24$), and p-tau217 (AUC 0.65, 95% CI 0.45–0.84, $p = 0.14$) did not discriminate between controls and any symptomatic FTD. Since p-tau217 concentrations were distinctively elevated in AmD and lvPPA, two phenotypes that often have primary AD as the underlying cause, we tested the comparative ability of p-tau217 to discriminate them from controls or the rest of the FTD phenotypes. When used to discriminate between AmD plus lvPPA and controls, both p-tau-217 (AUC 0.91, 95% CI 0.8–1, $p = 0.0004$, 70% sensitivity, 100% specificity) and NfL (AUC of 0.92, 95% CI 0.86–0.98, $p < 0.0001$, 58% sensitivity, 96% specificity) showed excellent discrimination (Figure S2). In contrast, $A\beta_{42}/A\beta_{40}$ showed only fair discrimination between AmD plus lvPPA and controls (AUC 0.74, 95% CI 0.6–0.89, $p = 0.0017$, 90.2% sensitivity, 29% specificity). The diagnostic performance of plasma p-tau217 to discriminate between AmD plus lvPPA vs. controls was superior when directly compared to $A\beta_{42}/A\beta_{40}$ (AUC 0.997, standard error = 0.004, $p < 0.0001$). When used to discriminate between AmD plus lvPPA and other symptomatic FTD phenotypes, p-tau217 showed good performance (AUC 0.86, (95% CI 0.75–0.96, $p < 0.0001$, 70% sensitivity, 92% specificity), whereas that of $A\beta_{42}/A\beta_{40}$ and NfL was only fair ($A\beta_{42}/A\beta_{40}$: AUC 0.73, 95% CI 0.61–0.85, $p = 0.0003$, 94% sensitivity, 29% specificity; NfL: AUC 0.6, 95% CI 0.5 to 0.72, $p = 0.13$, 68% sensitivity, 40% specificity).

3.3 | Baseline associations with clinical scales

In the whole cohort, at baseline, $A\beta_{42}/A\beta_{40}$ did not correlate with any clinical scale (Figure 2, Table S1). High p-tau217 was associated with worse disease severity (CDR+NACC/FTLDsb $\beta = 0.48$, 95% CI 0.06–2.9, $p = 0.05$), global cognition (MoCA $\beta = -5.6$, 95% CI −8 to −4, $p < 0.0001$), and verbal memory (CVLT recall $\beta = -1.52$, 95% CI −2.5 to −0.5, $p = 0.01$), but not with motor function or social cognition scores. High NfL was strongly associated with worse disease severity ($\beta = 2.29$, 95% CI 1.5–3, $p < 0.0001$), global cognition ($\beta = -3.71$, 95% CI −5 to −2.6, $p < 0.0001$), verbal memory ($\beta = -0.82$, 95% CI −1.4 to −0.3, $p = 0.01$), and social cognition (RSMS $\beta = -7.33$, 95% CI −9.8 to −5, $p = 0.01$), but not with motor function. When analyzed by phenotype, none of the biomarkers related to disease severity, with the exceptions of positive relationships with p-tau217 in bvFTD and CBS and with NfL in bvFTD and svPPA (Table S2).

3.4 | Prediction of longitudinal change in clinical scales

In a longitudinal analysis, in the whole cohort, baseline $A\beta_{42}/A\beta_{40}$ did not relate to changes in any clinical scale. High baseline p-tau217, however, was associated with more severe decline in global cognition ($\beta = -5.63$, 95% CI −7.7 to −3.5, $p < 0.0001$) and verbal memory ($\beta = -1.52$, 95% CI −2.5 to −0.5, $p = 0.003$), compared to low baseline p-tau217 (Figure 3, Table S3). High baseline NfL was associated with faster decline in disease severity ($\beta = 1.2$, 95% CI 0.42–2, $p = 0.004$), global cognition ($\beta = -2.6$, 95% CI −3.6 to −1.5, $p < 0.0001$), social cognition ($\beta = -4.7$, 95% CI −6.9 to −2.5, $p < 0.0001$), and verbal memory ($\beta = -0.75$, 95% CI −1.3 to −0.24, $p = 0.004$), compared to low baseline NfL.

3.5 | Associations with brain volumes

A total of 137 cases had brain volumes assessed by MRI. There were no associations between $A\beta_{42}/A\beta_{40}$ and brain volumes. High p-tau217 correlated with low right supramarginal gyrus ($\beta = -140.7$, 95% CI −264 to −17, $p = 0.03$), right hippocampus ($\beta = -93.9$, 95% CI −174 to −14, $p = 0.02$), and left hippocampus ($\beta = -91.2$, 95% CI −165 to −18, $p = 0.02$) volumes. High NfL strongly correlated with low volumes of all analyzed composites and individual regions (Figure 4 and Tables S4 and S5).

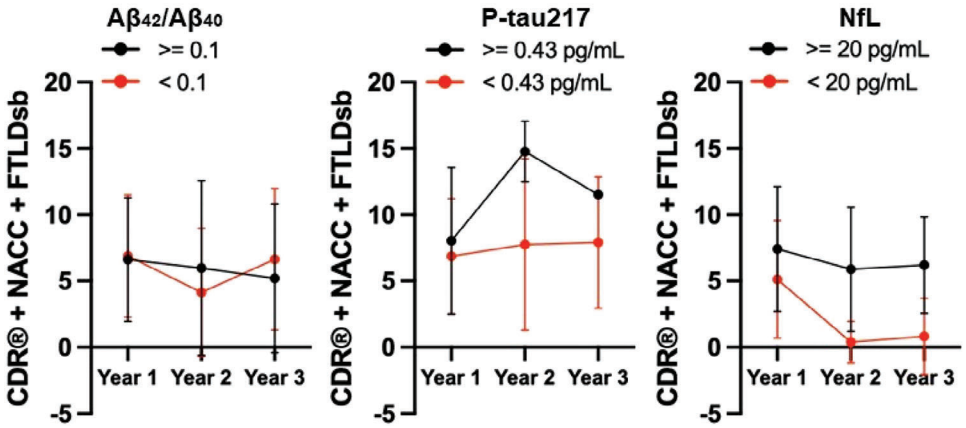

FIGURE 3 Associations between baseline plasma biomarkers and longitudinal disease severity measured with the CDR+NACC/FTLDsb, whole cohort. CDR, Clinical Dementia Rating; FTLDsb, Frontotemporal Lobar Degeneration module sum of boxes; NACC, National Alzheimer's Disease Coordinating Center.

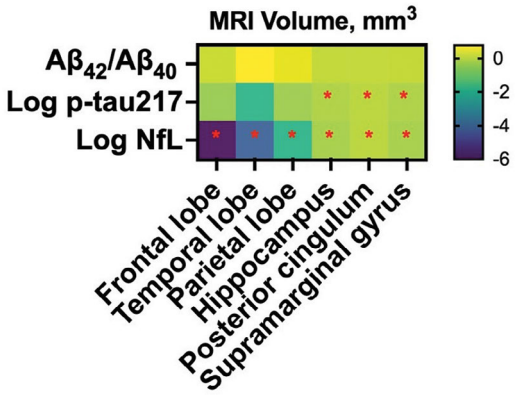

FIGURE 4 Correlation between baseline plasma biomarker concentrations and regional brain volumes assessed by MRI. The heatmaps show standardized beta coefficients for the associations between biomarker concentrations and MRI brain volumes. The scale shows positive coefficients in yellow and negative coefficients in purple. Asterisks indicate statistically significant correlations.

3.6 | Associations with FTLD neuropathological diagnosis and AD co-pathology

Thirty-eight cases (median age 61 ± 9 years) had autopsy data with confirmed neuropathological diagnoses. The most common primary diagnosis was FTLD-tau (53%), followed by FTLD-TDP (26%). The rest (11.5%) included FET, ubiquitin proteasome system (UPS), or unclassifiable FTLD. Two cases actually had primary AD pathology, and one case had Lewy body disease (Table S6). There were no differences in plasma $A\beta_{42}/A\beta_{40}$, p-tau217, or NfL concentrations by primary neuropathology diagnosis (Figures S3 and S4). Also, regardless of the primary neuropathological diagnosis, there were no significant changes in $A\beta_{42}/A\beta_{40}$, p-tau217, or NfL with increasing AD co-pathology scores (Figure S5). After correction for sex, age, and the interval between plasma sample collection and death, only p-tau217 was associated with more severe Braak stages ($\beta = 2.11$, 95% CI 0.1–4.1, $p = 0.05$) (Table 2).

4 | DISCUSSION

This study investigated the clinical value of plasma biomarkers of amyloid ($A\beta_{42}/A\beta_{40}$), tau (p-tau217), and neurodegeneration (NfL) in a cohort of clinically-diagnosed sporadic FTD cases, including a sub-cohort of neuropathologically-confirmed FTLD cases. The analysis revealed significant differences in the clinical performance of the three biomarkers. Notably, $A\beta_{42}/A\beta_{40}$ was lower in *APOEε4* carriers but did not differentiate between FTD phenotypes and was not associated with baseline or longitudinal clinical measures of disease severity, brain volumes, or AD co-pathology scores. In contrast, high p-tau217 was not only observed in *APOEε4* carriers but also in participants with AmD and lvPPA, two phenotypes in the FTD spectrum, but also strongly associated with AD pathology, and not in other FTD phenotypes. The p-tau217 correlated with global cognition and verbal memory at baseline and predicted worsening of these cognitive measures at 3 years. Remarkably, p-tau217 did not correlate with FTD-specific disease severity, motor function, or social cognition. High p-tau217 correlated with low volumes in the hippocampus and supramarginal gyrus, two regions vulnerable in AD, but not with composites of frontal, temporal, parietal, or occipital volumes. There were no differences in $A\beta_{42}/A\beta_{40}$, p-tau217, or NfL by primary FTLD diagnosis. After adjusting for sex, age, and the interval between plasma sample collection and death, only p-tau217 showed an association with more severe Braak stages, reflective of high tau burden. Finally, NfL was not influenced by the *APOE* genotype, but it was elevated across all symptomatic FTD phenotypes compared to controls, and strongly correlated, at baseline and longitudinally, with all clinical measures of disease severity, except for motor function. NfL also correlated with volumes of all analyzed brain regions. Taken together, the findings suggest that, when sporadic FTD is suspected, plasma p-tau217, but not $A\beta_{42}/A\beta_{40}$ or NfL, has

TABLE 2 Relationship between plasma biomarkers and AD co-pathology scores.

Clinical scale	Biomarker + time between biomarker collection and death	Unstandardized beta	95% CI	*p*-value
ADNC	$A\beta_{42}/A\beta_{40}$ + time between biomarker collection and death	−0.16	−1.3, 1	0.79
Braak	$A\beta_{42}/A\beta_{40}$ + time between biomarker collection and death	−0.66	−2.8, 1.5	0.56
Thal	$A\beta_{42}/A\beta_{40}$ + time between biomarker collection and death	0.09	−1.8, 2.02	0.93
ADNC	p-tau217+ time between biomarker collection and death	1.00	−0.07, 2.1	0.08
Braak	p-tau217+ time between biomarker collection and death	2.11	0.1, 4.1	0.05
Thal	p-tau217+ time between biomarker collection and death	1.10	−0.7, 2.9	0.25
ADNC	NfL+ time between biomarker collection and death	0.53	−0.3, 1.3	0.21
Braak	NfL+ time between biomarker collection and death	0.11	−1.4, 1.7	0.89
Thal	NfL+ time between biomarker collection and death	0.74	−0.6, 2.08	0.29

Note: Beta coefficients show associations corrected for age, sex, and interval between plasma collection and death.
Abbreviations: $A\beta_{42}/A\beta40$, amyloid $beta_{42}$/amyloid $beta_{40}$; AD, Alzheimer's disease; ADNC, Alzheimer's disease and related neurodegenerative conditions; CI, confidence interval.

meaningful associations with clinical, neuroimaging, and neuropathological features of AD, when present as a co-pathology, independent of the primary FTLD pathology.

Plasma p-tau217 has previously shown robust clinical associations in the AD clinical spectrum. It correlates with *APOEε4* carriership,[2] clinical disease severity and progression,[41] cognitive function,[6] brain atrophy in AD-vulnerable regions,[3] amyloid and tau[42,43] PET burden, and severity of AD neuropathology.[44] Plasma p-tau217 also offers excellent discrimination between neuropathology-confirmed AD and FTLD,[2] identifies amyloid PET-positive individuals among people with different types of dementia,[3] and has value for estimating the primary pathology of phenotypes that could be caused by AD or FTLD, such as CBS.[45] The current study contributes evidence that plasma p-tau217 has potential value for the identification of AD co-pathology in the setting of primary FTLD. The presence of AD co-pathology, as assessed by plasma p-tau217, seems to have clinical and neuroimaging correlates. Contrary to p-tau217, our study did not detect the same degree of clinicopathological associations for $A\beta_{42}/A\beta_{40}$ within the FTD cohort, which is consistent with other comparative studies between amyloid and tau biomarkers.[46,47] Of note, $A\beta_{42}/A\beta_{40}$ was lower in *APOEε4* carriers and showed numerical trends to be lower in participants with AmD and lvPPA phenotypes, the two clinical groups in which p-tau217 was significantly elevated. The reason for the better reflection of AD clinicopathological features by p-tau217 is not clear, but it may be related to a tighter relationship between tau burden and neurodegeneration, the types of analytes measured, the sensitivity of the platforms used for their quantification, or FTLD-specific factors that accentuate or mitigate disease expression and the clinicopathological associations of the biomarkers. For example, AD co-pathology has been shown to modulate the clinical presentation of four-repeat tauopathies, with less severe motor impairment and more severe functional dissociations in the default-mode network.[48] We observed no added value of NfL to track AD co-pathology, but our data are certainly in line with previous studies that have established its value for the identification of symptomatic disease and its robust clinical and imaging associations in FTD.[10,40,49]

Our findings may have diagnostic and management implications. Coexistence of AD with other neurodegenerative disorders is common. With the introduction of plasma AD biomarkers into clinical practice, increasing numbers of positive AD biomarkers will be seen in the setting of phenotypes that are suspected to be due to FTLD. Detection of plasma p-tau217 may help clinicians redefine their diagnostic impressions, just as it has been demonstrated with the introduction of amyloid PET.[50] Physicians may also increase their index of clinical suspicion around the presence of AD co-pathology, especially in phenotypes in which the prediction of FLTD primary pathology can be done with more confidence, such as PSP-RS or FTD/ALS. Although the distinction between primary AD pathology and AD as a co-pathology in primary FTLD may still not be possible, new avenues of inquiry may aim to better characterize clinical trajectories and investigate the biomarker evidence of AD as a management target, potentially allowing for personalized treatment strategies in FTD. It is possible that plasma p-tau217 could assist in selecting cases for FTD clinical trials, allowing for trial designs that account for the potential presence of AD co-pathology.

This study has a number of limitations. Longitudinal, neuroimaging, and neuropathological data were limited, which may restrict the ability to uncover other important clinical associations. Further validation of the results in a larger neuropathology-confirmed cohort is required. The demographic homogeneity of the studied population, mainly White and well-educated participants without major comorbidities, may limit the generalizability of the results to a broader and more diverse population. Generalizability is also limited by the lack of a replication cohort. Although state-of-the-art analytical platforms were used to quantify the biomarkers, even more precision may be required to determine clinically meaningful associations. Exploring other phosphorylated tau forms could offer further insights into the pathophysiology and progression of AD in the setting of FTLD. There is still a need for specific FTLD biomarkers, and more biomarker discovery efforts should be conducted.

In conclusion, this study supports the utility of plasma p-tau217 in identifying cases with neuropathologically confirmed

AD co-pathology in the setting of primary FTLD and may be of value as a clinical biomarker when FTD is suspected. Continuing this line of investigation is crucial for advancing personalized treatment strategies and ultimately enhancing patient care and outcomes.

AUTHOR CONTRIBUTIONS

Julio C. Rojas, Adam L. Boxer, and Binita Rajbanshi co-conceived the study. Binita Rajbanshi conducted statistical analyses and drafted the manuscript. Randall J. Bateman's team performed the mass spectrometry for Aβ_{42} and Aβ_{40}. All authors contributed a critical review of the manuscript.

ACKNOWLEDGMENTS

Patients and study companions enrolled in this study.

CONFLICT OF INTEREST STATEMENT

Binita Rajbanshi, Igor Prufer Q C Araujo, Lawren VandeVrede, Peter A. Ljubenkov, Hilary W. Heuer, Argentina Lario Lago, Leonard Petrucelli, Tania Gendron, William W. Seeley, Lea T. Grinberg, Salvatore Spina, Randall J. Bateman, Howard J. Rosen, Bradley F. Boeve, and Adam L. Boxer have no conflict of interest to disclose. Adam M. Staffaroni has received research support from the NIA/NIH, Bluefield Project to Cure FTD, the Alzheimer's Association, the Larry L. Hillblom Foundation, and the Rainwater Charitable Foundation, and has provided consultation to Alector, Lilly/Prevail, Passage Bio, and Takeda. Eliana Marisa Ramos receives research support from the NIH. Jeffrey L. Dage is an inventor on patents or patent applications of Eli Lilly and Company relating to the assays, methods, reagents and/or compositions of matter for p-tau assays and Aβ targeting therapeutics. He has served as a consultant or on advisory boards for Eisai, Abbvie, Genotix Biotechnologies Inc, Gates Ventures, Karuna Therapeutics, AlzPath Inc., Cognito Therapeutics, Inc., and received research support from ADx Neurosciences, Fujirebio, AlzPath Inc., Roche Diagnostics and Eli Lilly and Company in the past 2 years. He has received speaker fees from Eli Lilly and Company and is a founder and advisor for Monument Biosciences. Dr. Dage has stock or stock options in Eli Lilly and Company, Genotix Biotechnologies, AlzPath Inc. and Monument Biosciences. Julio C. Rojas is a site PI for clinical trials sponsored by Eli-Lilly, Eisai and Amylyx. He receives consulting fees from Roon Health, Inc and Ferrer International, S.A. This work was supported by K23AG059888, AlzOut and the John Douglas French Alzheimer's Foundation for J.C.R. Samples from the National Centralized Repository for Alzheimer Disease and Related Dementias (NCRAD), which receives government support under a cooperative agreement grant (U24 AG021886) awarded by the National Institute on Aging (NIA), were used in this study. The ALLFTD consortium is funded by the NIA and the National Institute of Neurological Diseases and Stroke (NINDS) (U19: AG063911). The former ARTFL and LEFFTDS consortia received funding from the NIA, NINDS and National Center for Advancing Translational Science (U54 NS092089, U01 AG045390). Author disclosures are present in supporting information.

CONSENT STATEMENT

All human subjects provided informed consent to participate in this study.

DATA AVAILABILITY STATEMENT

The datasets from this study are available upon reasonable request.

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SUPPORTING INFORMATION

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

How to cite this article: Rajbanshi B, Prufer Q C Araujo I, VandeVrede L, et al. Clinical and neuropathological associations of plasma $A\beta_{42}/A\beta_{40}$, p-tau217 and neurofilament light in sporadic frontotemporal dementia spectrum disorders. *Alzheimer's Dement*. 2025;17:e70078. https://doi.org/10.1002/dad2.70078