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RESEARCH ARTICLE

Plasma p-tau$_{217}$ and neurofilament/p-tau$_{217}$ ratio in differentiating Alzheimer's disease from syndromes associated with frontotemporal lobar degeneration

Alberto Benussi[1] | **Hanna Huber**[2] | **Kübra Tan**[2] | **Valentina Cantoni**[3] | **Jasmine Rivolta**[3] | **Maria Sofia Cotelli**[3] | **Andrea L. Benedet**[2] | **Kaj Blennow**[2,4,5,6] | **Henrik Zetterberg**[2,7,8,9,10] | **Nicholas J. Ashton**[2,11,12] | **Barbara Borroni**[13,14]

[1]Neurology Unit, Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy

[2]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska, Academy, University of Gothenburg, Gothenburg, Sweden

[3]Cognitive and Behavioural Neurology Unit, Department of Continuity of Care and Frailty, ASST Spedali Civili di Brescia, Brescia, Italy

[4]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

[5]Paris Brain Institute, ICM, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France

[6]Neurodegenerative Disorder Research Center, Division of Life Sciences and Medicine, and Department of Neurology, Institute on Aging and Brain Disorders, University of Science and Technology of China and First Affiliated Hospital of USTC, Hefei, P.R. China

[7]Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK

[8]UK Dementia Research Institute, Department of Molecular Neuroscience, UCL, London, UK

[9]Hong Kong Center for Neurodegenerative Diseases, Division of Life Science, Clear Water Bay, Hong Kong, China

[10]Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin–Madison, Madison, Wisconsin, USA

[11]Banner Sun Health Research Institute, Sun City, Arizona, USA

[12]Banner Alzheimer's Institute, Phoenix, Arizona, USA

[13]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

[14]Molecular Markers Laboratory, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

Correspondence
Barbara Borroni, Department of Clinical and Experimental Sciences, University of Brescia, Piazzale Spedali Civili 1, 25123 Brescia, Italy.
Email: bborroni@inwind.it

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Abstract

INTRODUCTION: Plasma-based biomarkers have shown promise for clinical implementation, but their accuracy in differentiating Alzheimer's disease (AD) from syndromes associated with frontotemporal lobar degeneration (FTLD) has yet to be fully investigated. This study assessed the potential of plasma biomarkers for differential diagnosis.

METHODS: This cohort study included 374 participants (96 AD, 278 FTLD). Plasma phosphorylated tau (p-tau)$_{217}$, neurofilament light chain (NfL), brain-derived tau, glial fibrillary acidic protein, and the amyloid beta$_{1\text{-}42}$/$_{1\text{-}40}$ ratio were measured. Receiver

Alberto Benussi and Hanna Huber contributed equally to this work (shared first author).

Nicholas J. Ashton and Barbara Borroni contributed equally to this work (shared last author).

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operating characteristic curve analyses assessed diagnostic accuracy, and a three-range threshold approach was used to stratify patients based on the most accurate biomarker.

RESULTS: Plasma p-tau$_{217}$ effectively distinguished AD from FTLD, with the NfL/p-tau$_{217}$ ratio showing superior accuracy. The three-range approach identified thresholds with 95% and 97.5% sensitivity and specificity, reducing the need for cerebrospinal fluid testing by 75% and 54%, respectively.

DISCUSSION: Plasma p-tau$_{217}$ and the NfL/p-tau$_{217}$ ratio are promising non-invasive biomarkers for differentiating AD from FTLD, suggesting their use as a potential alternative to traditional diagnostic methods.

KEYWORDS
Alzheimer's disease, blood-based biomarkers, diagnostic accuracy, frontotemporal lobar degeneration, neurofilament light chain, phosphorylated tau217

Highlights

- Plasma phosphorylated tau (p-tau)$_{217}$ distinguishes Alzheimer's disease (AD) from frontotemporal lobar degeneration (FTLD) with high accuracy.
- The neurofilament light chain/p-tau$_{217}$ ratio showed the highest accuracy for differentiating AD from FTLD.
- A three-range threshold reduces the need for invasive cerebrospinal fluid testing or amyloid positron emission tomography imaging.

1 | BACKGROUND

Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) are the two most common causes of early-onset dementia.[1] Both conditions exhibit distinct pathological and clinical features, necessitating different therapeutic approaches. The ability to accurately and differentiate early between these diseases is crucial for effective management and treatment, particularly with the advent of new disease-modifying therapies.[2,3] Currently, the diagnostic process relies heavily on clinical assessments, neuroimaging, and cerebrospinal fluid (CSF) biomarkers.[4] However, these methods are often invasive, costly, and not widely accessible. Thus, there is an increasing demand for non-invasive, cost-effective blood-based biomarkers that can aid in the differential diagnosis of AD and FTLD-associated syndromes.[5,6]

While specific biomarkers for FTLD-associated syndromes are lacking, AD-related biomarkers may be used to rule out AD in the differential diagnosis between AD and FTLD. There are specific plasma biomarkers that have been closely associated with AD pathology, including phosphorylated tau (p-tau), brain-derived tau (BD-tau), amyloid beta (Aβ),[7–17] and glial fibrillary acidic protein (GFAP).[18–21] In particular, among forms of phosphorylated tau, p-tau$_{217}$ has shown significant promise due to its high specificity and sensitivity for AD.[10–13]

Most studies on plasma biomarkers have focused on distinguishing AD or mild cognitive impairment (MCI) from healthy aging, on predicting conversion from MCI to AD, or correlating biomarkers with AD-related pathologies, such as Aβ and tau deposition.[12,15,17] However, only a few reports have investigated blood-based biomarker performance in distinguishing AD from syndromes associated with FTLD, and biomarker potential for differential diagnosis has yet to be fully explored.[13,22]

In addition to these AD-specific biomarkers, neurofilament light chain (NfL) is indicative of broader neurodegenerative processes.[23–25] This marker is elevated in a range of neurodegenerative diseases, including both AD and FTLD, but its expression levels can vary significantly between these conditions. For instance, NfL tends to be higher in FTLD and amyotrophic lateral sclerosis compared to AD[23–25]; thus, the distinct differences in their levels between these diseases can be leveraged in diagnostic algorithms.

These observations prompted the present study, aimed to evaluate not only the diagnostic accuracy of plasma p-tau$_{217}$ in differentiating AD from FTLD but also to compare it to other plasma biomarkers such as NfL, BD-tau, GFAP, and A$\beta_{1\text{-}42}$/A$\beta_{1\text{-}40}$ ratio. By doing so, we aim to identify the best single biomarker or combination of biomarkers that offers the highest diagnostic accuracy for the differential diagnosis between AD and FTLD. Additionally, we will assess the utility of a three-range threshold approach to stratify patients into low-, intermediate-, and high-risk groups[26] based on the most accurate biomarker, potentially reducing the need for more invasive diagnostic procedures.

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2 | METHODS

2.1 | Participants

This cohort study involved participants recruited from the Centre for Neurological Disorders at the University of Brescia, Italy. The included participants met the current clinical criteria for probable AD[27] or an FTLD-associated syndrome, including the behavioral variant of frontotemporal dementia (bvFTD),[28] the agrammatic or semantic variant of primary progressive aphasia (PPA),[29] corticobasal syndrome (CBS),[30] or progressive supranuclear palsy (PSP).[31] All participants underwent an extensive neuropsychological evaluation, following standard procedures, as previously reported.[32,33] Disease severity was assessed with the Clinical Dementia Rating (CDR)[34] or with the CDR plus National Alzheimer's Coordinating Center (NACC) behavior and language domains (CDR plus NACC FTLD) global score.[35,36] A subgroup of participants with a global CDR or CDR plus NACC FTLD score = 0.5 was selected to analyze the accuracy of blood biomarkers in the early phases of the disease, such as MCI for AD,[37] or mild cognitive, behavioral, and motor impairment (MCBMI) for FTLD.[38,39]

Brain magnetic resonance imaging scans were performed on all participants. For a subgroup of participants, the diagnosis was confirmed with amyloid markers, including CSF total tau, p-tau$_{181}$, and A$\beta_{1\text{-}42}$ determinations (n = 193), or amyloid positron emission tomography (PET) imaging with [^{18}F]-florbetapir or [^{18}F]-flutemetamol (n = 64), either supporting or ruling out an AD diagnosis, as previously reported.[40] When diagnostic confidence in selected cases was not satisfactory, additional procedures, including brain fluorodeoxyglucose PET, were used. Furthermore, in familial cases (defined by the presence of at least one dementia case among the first-degree relatives) and early onset sporadic cases, genetic screening for monogenic forms of frontotemporal dementia (FTD), such as *GRN*, *C9orf72*, and *MAPT* variants, was performed.

Moreover, a group of age-matched healthy controls (HCs) was also enrolled as the reference group. HCs underwent a brief standardized neuropsychological assessment, with a Mini-Mental State Examination (MMSE) score of ≥ 27/30 required for inclusion. Psychiatric or other neurological illnesses were considered exclusion criteria.

Full written informed consent was obtained from all subjects according to the Declaration of Helsinki. The study protocol was approved by the Brescia Ethics Committee.

2.2 | Biomarkers assays

Plasma samples were collected according to standard procedures and stored at −80°C until use. Biological analyses were carried out at the University of Gothenburg, Sweden. Plasma NfL, GFAP, A$\beta_{1\text{-}42}$, and A$\beta_{1\text{-}40}$ were quantified using the commercial Neurology 4-plex E kit (103670; Quanterix), as previously published.[11] Plasma p-tau$_{217}$ was quantified using the ALZpath Quanterix[11] and BD-tau was measured using validated in-house assays.[14] Samples were run in duplicate on a Quanterix Simoa-HD-X platform in one round of experiments with intra- and inter-assay variation < 15% for all biomarkers.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using PubMed and other relevant sources to investigate the use of plasma biomarkers in differentiating Alzheimer's disease (AD) from frontotemporal lobar degeneration (FTLD). While plasma biomarkers have been studied for distinguishing AD from healthy aging or predicting disease progression, their use in differentiating AD from FTLD has been less explored. This study addresses this gap by evaluating the diagnostic accuracy of plasma phosphorylated tau (p-tau)$_{217}$ and other blood-based biomarkers.
2. **Interpretation**: The study demonstrates that plasma p-tau$_{217}$ and the neurofilament light chain/p-tau$_{217}$ ratio provide high diagnostic accuracy in distinguishing AD from FTLD syndromes. These biomarkers could potentially serve as non-invasive alternatives to cerebrospinal fluid testing, reducing the need for more invasive diagnostic procedures.
3. **Future directions**: Future research should include multicenter studies with larger, diverse populations to confirm these findings; assess longitudinal utility in disease monitoring; and explore combined biomarker use for enhanced diagnostic accuracy.

2.3 | Statistical analysis

Baseline demographic variables across groups were compared using the Kruskal–Wallis H test or Fisher exact test, as appropriate. To compare plasma biomarker levels between groups we used a non-parametric analysis of covariance (ANCOVA) using a Quade test,[41] adjusting for age. For post hoc pairwise comparisons between groups, Cohen d was calculated to measure effect size. Effect sizes were interpreted as small (d = 0.2), medium (d = 0.5), and large (d = 0.8). Bivariate correlations between plasma values and clinical characteristics were assessed using Spearman rank correlation coefficients (r_s). To assess whether the correlations between biomarkers and clinical variables differed between the groups, we performed Fisher Z tests on the Spearman correlation coefficients obtained for each group.

Receiver operating characteristic (ROC) curve analyses were plotted, and the area under the curve (AUC), including 95% confidence interval (CI) values, were reported. Differences between AUC values were tested using DeLong statistics.[42] Cut-off values that maximized Youden index were used to determine sensitivity and specificity.[43]

To identify a three-range classification system based on the most accurate biomarker, we aimed to stratify patients into low-, intermediate-, and high-risk groups for AD versus FTLD-associated syndromes. We performed a binary logistic regression analysis to evaluate the association between the most accurate biomarker and the

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TABLE 1 Demographic and clinical characteristics of included participants.

	AD ($n = 96$)	FTLD ($n = 278$)	HC ($n = 30$)
Age, y	71.0 (63.7–76.0)**	65.3 (59.3–71.7)*	65.4 (61.1–71.5)
Age at onset, y	68.0 (61.0–73.0)**	62.0 (55.9–68.3)*	–
Sex, female, *n* (%)	50 (52.1%)	115 (41.4%)	18 (60.0%)
Education, y	10.0 (7.3–13.0)	11.0 (8.0–13.0)	11.0 (8.0–14.5)
MMSE score	23.0 (22.0–26.0)***	24.0 (19.0–27.0)***	27.0 (27.0–28.0)*,**
CDR	0.5 (0.5–1.0)	–	–
CDR plus NACC FTLD	–	1.0 (0.5–2.0)	–
Plasma biomarkers			
p-tau$_{217}$ (pg/mL)	1.23 (0.84–1.74)**,***	0.27 (0.14–0.43)*	0.32 (0.22–0.51)*
BD-tau (pg/mL)	1.56 (1.18–2.03)**	0.76 (0.39–1.40)*	1.07 (0.74–1.36)
NfL (pg/mL)	28.31 (21.54–36.21)**,***	48.93 (30.58–83.54)*,***	17.76 (12.00–25.13)*,**
GFAP (pg/mL)	324.41 (241.4–436.56)**,***	226.62 (158.59–323.24)*	217.36 (150.00–292.01)*
A$\beta_{1\text{-}40}$ (pg/mL)	106.00 (68.90–133.00)**	64.40 (32.55–110.25)*,***	105.50 (87.50–138.75)**
A$\beta_{1\text{-}42}$ (pg/mL)	5.24 (3.66–7.19)***	4.60 (2.68–8.07)***	8.64 (6.49–11.18)*,**
A$\beta_{1\text{-}42/1\text{-}40}$ ratio	0.053 (0.045–0.060)**,***	0.075 (0.060–0.107)*	0.074 (0.065–0.105)*

Note: Data are median (IQR) or *n* (%).
Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; BD-tau, brain-derived tau; CDR plus NACC FTLD, Clinical Dementia Rating plus National Alzheimer's Coordinating Center behavior and language domains; CDR, Clinical Dementia Rating scale; FTLD, frontotemporal lobar degeneration; GFAP, glial fibrillary acidic protein; HC, healthy control; IQR, interquartile range; MMSE, Mini-Mental State Examination; *n*, number of patients; NfL, neurofilament light chain; p-tau, phosphorylated tau; y, years.
*$p < 0.05$ versus AD.
**$p < 0.05$ versus FTLD.
***$p < 0.05$ versus HC, pairwise comparisons after significant interaction at the Kruskal–Wallis *H* test or at the Fisher exact test, while plasma biomarker levels were compared using the rank-based non-parametric analysis of covariance (ANCOVA) method, with age as a covariate,[41] after adjustment by the false discovery rate correction for multiple comparisons.[44]

likelihood of FTLD diagnosis. These probabilities were then rescaled so that a probability of 0% represented the likelihood of AD, and 100% represented the likelihood of FTLD. We used the rescaled probabilities to identify the thresholds that achieved 95% and 97.5% sensitivity and specificity for diagnosing FTLD. The biomarker values corresponding to these thresholds were identified directly from the dataset. The number of participants in each risk category was calculated, allowing us to quantify the distribution across these three ranges and identify the group needing further analysis.

A two-sided p value < 0.05 was considered significant and corrected for multiple comparisons using the false discovery rate (FDR)[44] method, where appropriate. Data analyses were conducted using IBM SPSS Statistics version 29.0 (IBM Corp), MedCalc Statistical Software version 23.0 (MedCalc Software Ltd), and GraphPad Prism version 10.0 (GraphPad Software).

3 | RESULTS

3.1 | Participants

A total of 374 participants were included in the study, of whom 96 with AD (median [interquartile range (IQR)] age 71.0 [63.7–76.0] years; 50 females [52.1%]) and 278 with FTLD-associated syndromes (median [IQR] age 65.3 [59.3–71.7] years; 115 females [41.4%]). Among the FTLD group, 146 participants were classified as bvFTD (median [IQR] age 64.8 [57.8–71.4] years; 49 females [33.6%]), 92 as PPA (median [IQR] age 65.9 [59.5–72.4] years; 49 females [53.3%]), 22 as CBS (median [IQR] age 67.3 [62.3–73.2] years; 10 females [45.5%]), and 18 as PSP (median [IQR] age 66.9 [63.7–73.1] years; 7 females [38.9%]). A group of 30 age-matched HCs (median [IQR] age 65.4 [61.1–71.5] years; 18 females [60.0%]) was included as the reference group.

The demographic characteristics of the included participants are reported in Table 1. Briefly, participants with AD were significantly older than those with FTLD ($p < 0.001$) and had an older age at disease onset ($p < 0.001$; see Table 1).

3.2 | Plasma biomarkers

Given the disease-specific age differences among groups, plasma biomarker levels were age-corrected using a non-parametric ANCOVA. We observed significantly higher levels of plasma p-tau$_{217}$ in participants with AD compared to both the FTLD group ($p < 0.001$, $d = 1.334$) and HC group ($p < 0.001$, $d = 0.619$; see Figure 1A). Plasma BD-tau was also elevated in participants with AD compared to both FTLD ($p < 0.001$, $d = 0.674$) and HC ($p < 0.001$, $d = 0.225$); however, there was no significant difference between FTLD and HC ($p = 0.088$, $d = 0.171$;

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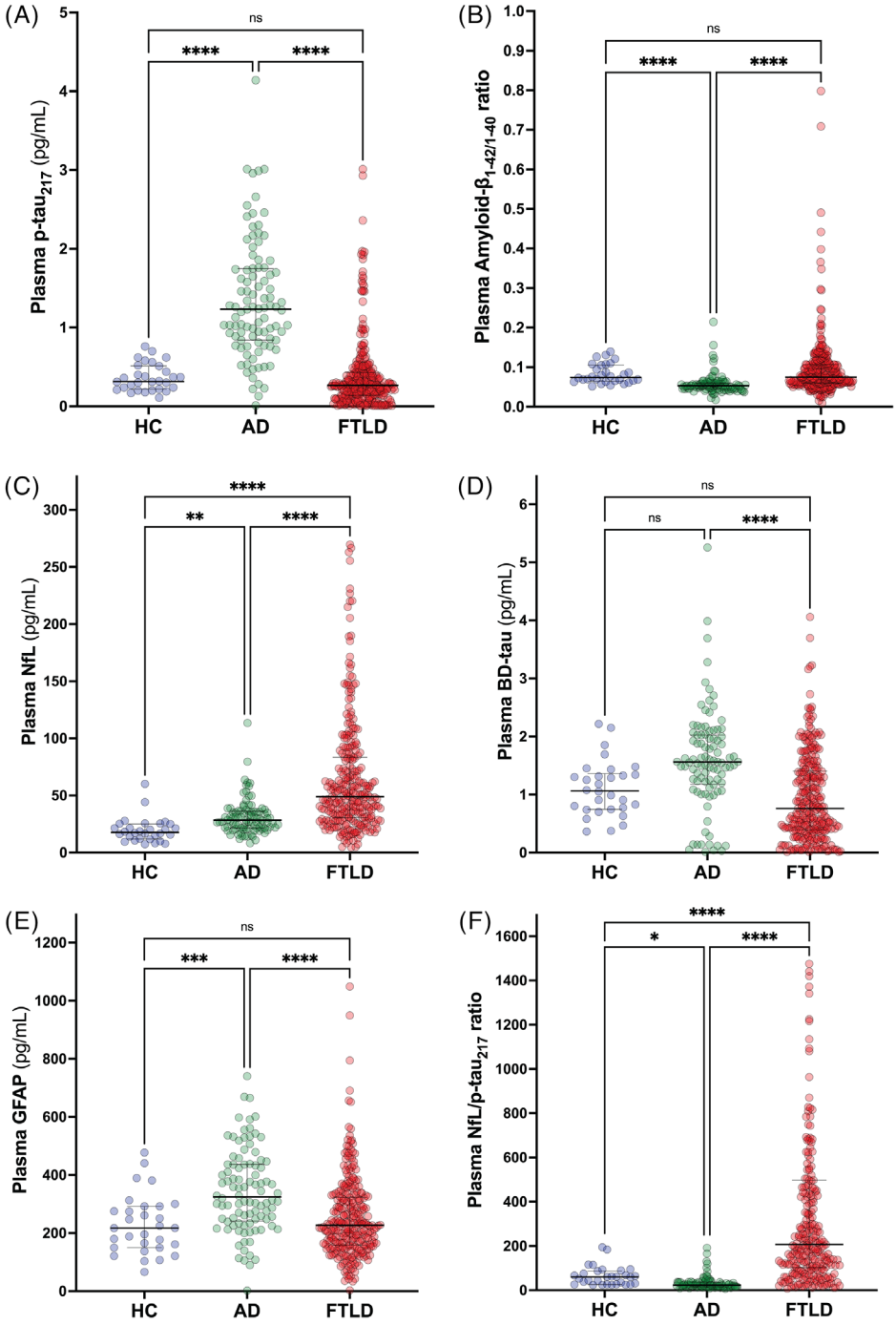

FIGURE 1 Plasma biomarker concentrations in participants by clinical diagnosis. A, Plasma p-tau$_{217}$. B, A$\beta_{1\text{-}42}$/A$\beta_{1\text{-}40}$ ratio. C, NfL. D, BD-tau. E, GFAP. F, NfL/p-tau$_{217}$ ratio in participants by clinical diagnosis. Thick horizontal lines represent median values while thin horizontal lines represent the interquartile range. $^{*}p < 0.05$, $^{**}p < 0.010$, $^{***}p < 0.001$. Aβ, amyloid beta; AD, Alzheimer's disease; BD-tau, brain-derived tau; FTLD, frontotemporal lobar degeneration; GFAP, glial fibrillary acidic protein; HC, healthy control; NfL, neurofilament light chain; ns, non-significant; p-tau, phosphorylated tau.

see Figure 1B). Plasma NfL levels were significantly higher in participants with FTLD compared to both AD ($p < 0.001$, $d = 0.814$) and HC ($p = 0.001$, $d = 0.868$), while participants with AD had higher levels compared to HC ($p = 0.001$, $d = 0.337$; see Figure 1C). Plasma GFAP levels were significantly increased in AD compared to both FTLD ($p < 0.001$, $d = 0.484$) and HC ($p < 0.001$, $d = 0.358$), with no significant difference observed between the latter two groups ($p = 0.358$, $d = 0.092$; see Figure 1D). The A$\beta_{1\text{-}42/1\text{-}40}$ ratio was significantly lower in participants with AD compared to both FTLD ($p < 0.001$, $d = 0.818$) and HC ($p < 0.001$, d = 0.525; see Figure 1E). We observed comparable results if only patients with a biomarker-supported diagnosis were considered (see Table S1 in supporting information).

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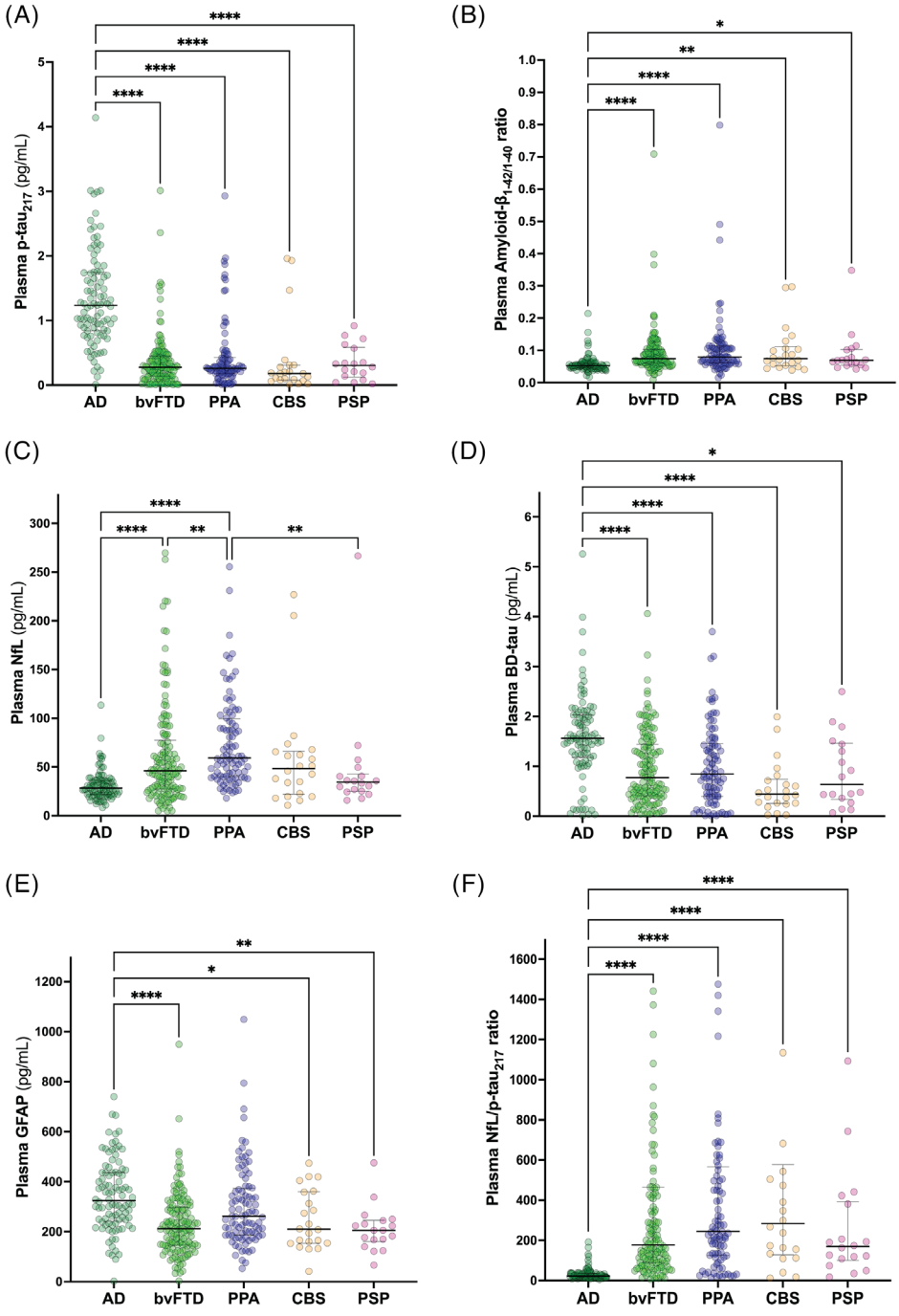

FIGURE 2 Plasma biomarker concentrations in participants by FTLD-associated syndromes subgroups. A, Plasma p-tau$_{217}$. B, A$\beta_{1\text{-}42}$/A$\beta_{1\text{-}40}$ ratio. C, NfL. D, BD-tau. E, GFAP. F, NfL/p-tau$_{217}$ ratio in participants by clinical diagnosis. Thick horizontal lines represent median values while thin horizontal lines represent the interquartile range. *$p < 0.05$, **$p < 0.010$, ***$p < 0.001$. Aβ, amyloid beta; AD, Alzheimer's disease; BD-tau, brain-derived tau; bvFTD, behavioral variant frontotemporal dementia; CBS, corticobasal syndrome; FTLD, frontotemporal lobar degeneration; GFAP, glial fibrillary acidic protein; HC, healthy control; NfL, neurofilament light chain; ns, non-significant; PPA, primary progressive aphasia; PSP, progressive supranuclear palsy; p-tau, phosphorylated tau.

When considering the FTLD subgroups, comprising participants with bvFTD, PPA, CBS, and PSP, similar results were observed for all plasma biomarkers compared to the AD group. Briefly, p-tau$_{217}$ levels were significantly higher in AD compared to all FTLD-associated syndromes (all $p < 0.001$), as were BD-tau levels (all $p < 0.050$). The A$\beta_{1\text{-}42/1\text{-}40}$ ratio was significantly lower (all $p < 0.050$), as were plasma NfL levels (all $p < 0.010$, except vs. CBS). Plasma GFAP levels were also significantly higher in AD (all $p < 0.050$, except vs. PPA; see Figure 2 and Table S2 in supporting information).

In the entire population, significant correlations were observed between plasma p-tau$_{217}$ and BD-tau ($r_s = 0.63$, $p < 0.001$), NfL ($r_s = -0.17$, $p < 0.001$), GFAP ($r_s = 0.45$, $p < 0.001$), A$\beta_{1\text{-}40}$ ($r_s = 0.56$,

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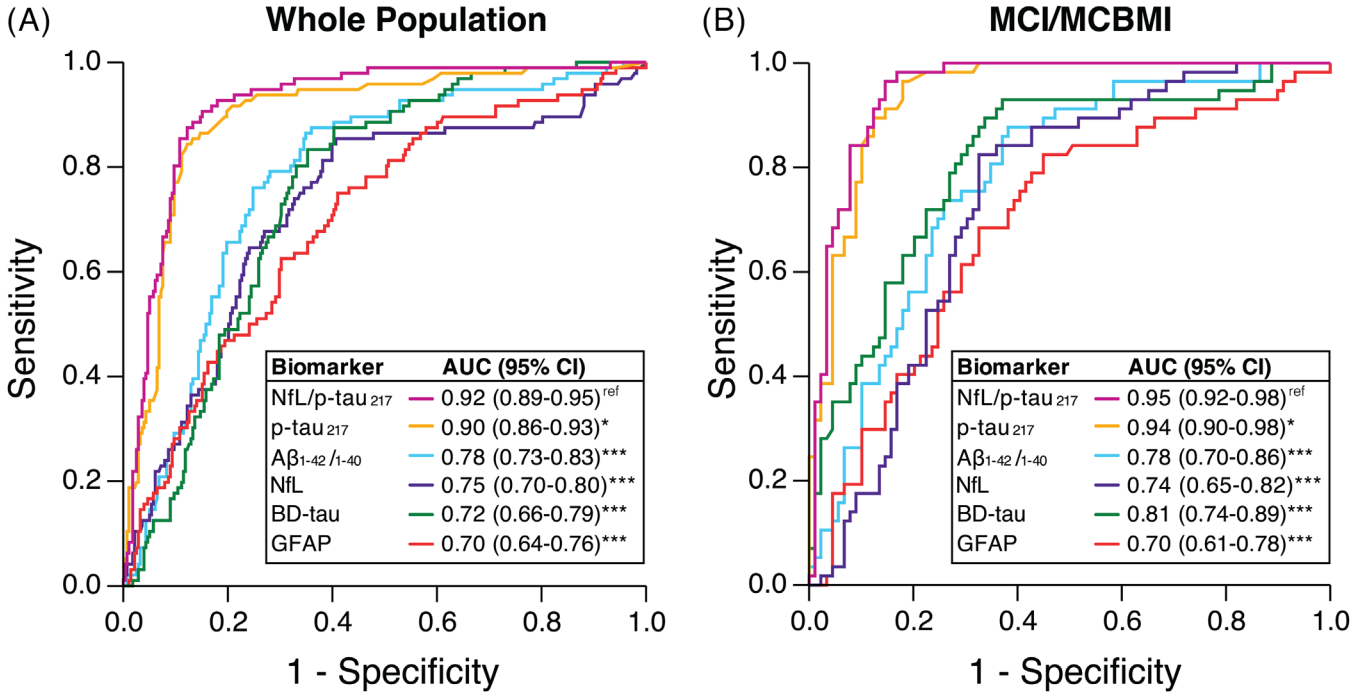

FIGURE 3 ROC curve analysis. ROC curves for differentiating participants with AD from FTLD in (A) the whole population and (B) in participants with MCI/MCBMI, with AUCs and 95% CI. Comparisons between AUCs were performed using DeLong statistics. 95% CI, 95% confidence interval; Aβ, amyloid beta; AD, Alzheimer's disease; AUC, area under the curve; $A\beta_{1\text{-}42}/_{1\text{-}40}$, amyloid$\beta_{1\text{-}42}$/amyloid$\beta_{1\text{-}40}$ ratio; BD-tau, brain-derived tau; FTLD, frontotemporal lobar degeneration; GFAP, glial fibrillary acidic protein; NfL, neurofilament light; ns, non-significant; p-tau$_{217}$, phosphorylated at the 217 residue; ROC, receiver operating characteristic. $^{*}p < 0.05$, $^{**}p < 0.010$, $^{***}p < 0.001$ compared to the most accurate biomarker (ref). Aβ, amyloid beta; AD, Alzheimer's disease; AUC, area under the curve; BD-tau, brain-derived tau; CI, confidence interval; FTLD, frontotemporal lobar degeneration; GFAP, glial fibrillary acidic protein; HC, healthy control; MCBMI, mild cognitive, behavioral, and motor impairment; MCI, mild cognitive impairment; NfL, neurofilament light chain; ns, non-significant; p-tau, phosphorylated tau.

$p < 0.001$), $A\beta_{1\text{-}42}$ ($r_s = 0.36$, $p < 0.001$), age ($r_s = 0.23$, $p < 0.001$), global CDR scores ($r_s = -0.13$, $p = 0.008$), and MMSE scores ($r_s = -0.13$, $p = 0.011$). Considering only participants with AD, we observed comparable findings, except for correlations with age, global CDR scores, and MMSE scores, which were not significant. In FTLD patients, similar correlations were observed, including with age, but not with global CDR plus NACC scores or MMSE scores. Fisher *Z* tests revealed significant differences in the correlations between plasma p-tau$_{217}$ and other biomarkers between AD and FTLD. In particular, we observed significant differences for NfL ($Z = 2.49$, $p = 0.013$), with a stronger correlation in AD; $A\beta_{1\text{-}40}$ ($Z = -2.83$, $p = 0.005$) and $A\beta_{1\text{-}42}$ ($Z = -2.14$, $p = 0.032$), both stronger in FTLD. No significant differences were found for BD-tau, GFAP, age, CDR, or MMSE.

3.3 | Diagnostic accuracy

We performed ROC curve analysis to identify the biomarker with the highest accuracy in distinguishing AD from FTLD patients. The single biomarker with the highest AUC was p-tau$_{217}$ (AUC 0.90, 95% CI: 0.86–0.93, $p < 0.001$), followed by the $A\beta_{1\text{-}42/1\text{-}40}$ ratio (AUC 0.78, 95% CI: 0.73–0.83, $p < 0.001$), NfL (AUC 0.75, 95% CI: 0.73–0.83, $p < 0.001$), BD-tau (AUC 0.72, 95% CI: 0.66–0.79, $p < 0.001$), and GFAP (AUC 0.70, 95% CI: 0.64–0.76, $p < 0.001$; see Figure 3A). Considering that participants with FTLD had significantly higher levels of plasma NfL but also lower levels of p-tau$_{217}$ compared to those with AD, we analyzed the NfL/p-tau$_{217}$ ratio. This ratio yielded the highest AUC of 0.92 (95% CI: 0.89–0.95), $p < 0.001$, which was significantly more accurate than the single most accurate biomarker, p-tau$_{217}$, according to the DeLong statistic ($p = 0.0349$; see Figure 3A). According to the Youden index, the p-tau$_{217}$ alone showed a sensitivity of 84.4% and a specificity of 87.8%, while NfL/p-tau$_{217}$ ratio showed a sensitivity of 90.6% and a specificity of 84.9%.

When we selected patients with a global CDR or CDR plus NACC FLTD score = 0.5 (i.e., MCI/MCBMI; AD $n = 57$, FTLD $n = 89$), we observed very similar results. In particular, the NfL/p-tau$_{217}$ ratio again showed the highest accuracy (AUC 0.95, 95% CI: 0.92–0.98, $p < 0.001$), followed by p-tau$_{217}$ (AUC 0.94, 95% CI: 0.90–0.98, $p < 0.001$), BD-tau (AUC 0.81, 95% CI: 0.74–0.89, $p < 0.001$), the $A\beta_{1\text{-}42/1\text{-}40}$ ratio (AUC 0.78, 95%: CI 0.70–0.86, $p < 0.001$), NfL (AUC 0.74, 95% CI: 0.65–0.82, $p < 0.001$), and GFAP (AUC 0.70, 95% CI: 0.61–0.78, $p < 0.001$; see Figure 3B). According to the Youden index, the NfL/p-tau$_{217}$ ratio demonstrated a sensitivity of 96.5% and a specificity of 85.4%, while p-tau$_{217}$ alone showed a sensitivity of 96.5% and a specificity of 82.0%.

If we considered only patients with a biomarker-supported diagnosis (AD $n = 87$, FTLD $n = 144$), we observed very similar results. In particular, the NfL/p-tau$_{217}$ ratio again showed the highest accuracy

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(AUC 0.94, 95% CI: 0.90–0.97, $p < 0.001$), followed by p-tau$_{217}$ (AUC 0.92, 95% CI: 0.89–0.96, $p < 0.001$), the A$\beta_{1\text{-}42/1\text{-}40}$ ratio (AUC 0.81, 95% CI: 0.75–0.87, $p < 0.001$), BD-tau (AUC 0.75, 95% CI: 0.68–0.82, $p < 0.001$), NfL (AUC 0.75, 95% CI: 0.69–0.81, $p < 0.001$), and GFAP (AUC 0.72, 95% CI: 0.65–0.79, $p < 0.001$). According to the Youden index, the NfL/p-tau$_{217}$ ratio demonstrated a sensitivity of 88.5% and a specificity of 87.5%, while p-tau$_{217}$ alone showed a sensitivity of 86.2% and a specificity of 88.9%.

3.4 | Risk stratification using a three-range approach

Based on the logistic regression analysis, thresholds corresponding to 95% sensitivity (NfL/p-tau$_{217}$ ratio = 23.89) and 95% specificity (NfL/p-tau$_{217}$ ratio = 101.64) were established, allowing patients to be stratified into low-, intermediate-, and high-risk groups for FTLD associated syndromes. A total of 66 participants were categorized into the low-risk group (53 AD, 13 FTLD), 93 patients were categorized into the intermediate-risk group (38 AD, 55 FTLD), and 215 patients were categorized into the high-risk group (5 AD, 210 FTLD; see Figure 4A). By categorizing patients into low- and high-risk groups, a total of 281 participants (58 AD, 223 FTLD) would not require further CSF testing. This approach results in a reduction of ≈ 75% in the number of CSF tests needed.

If we used a more stringent threshold of 97.5% sensitivity (NfL/p-tau$_{217}$ ratio = 17.16) and 97.5% specificity (NfL/p-tau$_{217}$ ratio = 165.49) for diagnosing FTLD, a total of 38 participants were categorized into the low-risk group (36 AD, 2 FTLD), 172 participants were categorized into the intermediate-risk group (60 AD, 112 FTLD), and 164 participants were categorized into the high-risk group (0 AD, 164 FTLD). This more stringent threshold would result in 202 participants (36 AD, 166 FTLD) not requiring further CSF testing, leading to a reduction of ≈ 54% in the number of CSF tests needed.

If we consider the best single biomarker, p-tau$_{217}$, thresholds corresponding to 95% sensitivity (p-tau$_{217}$ = 1.47) and 95% specificity (p-tau$_{217}$ = 0.36) were established, enabling the stratification of patients into low-, intermediate-, and high-risk groups for FTLD-associated syndromes. In this analysis, 48 participants were classified into the low-risk group (34 AD, 14 FTLD), 135 into the intermediate-risk group (57 AD, 78 FTLD), and 191 into the high-risk group (5 AD, 186 FTLD; see Figure 4B). By categorizing patients into low- and high-risk groups, a total of 239 participants (39 AD, 200 FTLD) would not require further CSF testing, resulting in a reduction of ≈ 64% in the number of CSF tests needed.

By applying a more stringent threshold of 97.5% sensitivity (p-tau$_{217}$ = 1.87) and 97.5% specificity (p-tau$_{217}$ = 0.22) for diagnosing FTLD, the analysis stratified 26 participants into the low-risk group (19 AD, 7 FTLD), 233 participants into the intermediate-risk group (75 AD, 158 FTLD), and 115 participants into the high-risk group (2 AD, 113 FTLD). Using these thresholds, 141 participants (21 AD, 120 FTLD) could potentially avoid further CSF testing, resulting in a reduction of ≈ 31% in the number of CSF tests required.

The application of a three-range approach using the NfL/p-tau$_{217}$ ratio at a 95% sensitivity and specificity threshold resulted in an ≈ 11% reduction in the need for CSF tests compared to using p-tau$_{217}$ alone. Moreover, applying a 97.5% sensitivity and specificity threshold could reduce the required CSF testing by ≈ 23%.

4 | DISCUSSION

With the rising prevalence of dementia and the advent of disease-modifying therapies, there is a critical need for early and accurate diagnosis of neurodegenerative diseases. Current diagnostic approaches, including neuroimaging and CSF biomarkers, are often invasive, costly, and not readily available in all clinical settings.[45] Plasma biomarkers offer a promising alternative due to their non-invasive nature, ease of collection, and potential for widespread implementation in both primary and secondary care settings.

This study presents a comprehensive evaluation of plasma biomarkers in differentiating AD from FTLD, specifically focusing on plasma p-tau$_{217}$ and other markers such as NfL, BD-tau, GFAP, and the A$\beta_{1\text{-}42}$/$_{1\text{-}40}$ ratio.

The findings indicate that plasma p-tau$_{217}$ is highly effective in distinguishing AD from FTLD, demonstrating very high diagnostic accuracy compared to other available plasma biomarkers. Our results are consistent with previous studies showing the strong performance of p-tau$_{217}$ in detecting biological AD,[11] and further demonstrate that p-tau$_{217}$ is a valuable tool for the differential diagnosis between FTLD-associated syndromes and AD.

Additionally, we assessed the added clinical utility of combining biomarkers, and found that the NfL/p-tau$_{217}$ ratio demonstrated superior accuracy compared to any single biomarker, making it a particularly promising tool for differential diagnosis. NfL, a marker of neuronal damage,[23–25] was significantly higher in FTLD compared to both AD and HCs. While this makes NfL a valuable indicator for distinguishing FTLD from AD, its known variability suggests that it should not be relied upon in isolation for differential diagnosis.[46] Instead, NfL may be most effective when used in conjunction with other biomarkers, such as plasma p-tau$_{217}$.

While the p-tau$_{217}$/NfL ratio demonstrated the highest AUC (0.92) compared to p-tau$_{217}$ alone (AUC 0.90), the difference, although statistically significant, is modest. The slightly lower specificity of the ratio suggests that, depending on the clinical context, p-tau$_{217}$ alone may still be a highly effective biomarker for distinguishing AD from FTLD.

While our study focused on distinguishing AD from FTLD, in clinical practice, patients often present with overlapping symptoms. Several studies have shown that patients with a clinical diagnosis of AD may have underlying FTLD pathology, and vice versa.[47,48] The p-tau$_{217}$/NfL ratio may be particularly useful in these diagnostically challenging cases, in which non-invasive biomarkers can help clarify the underlying pathology and guide further diagnostic steps, potentially reducing the need for invasive procedures.

An interesting finding was that, although the A$\beta_{1\text{-}42}$/$_{1\text{-}40}$ ratio was lower in AD, plasma A$\beta_{1\text{-}42}$ levels were higher in AD than FTLD. This

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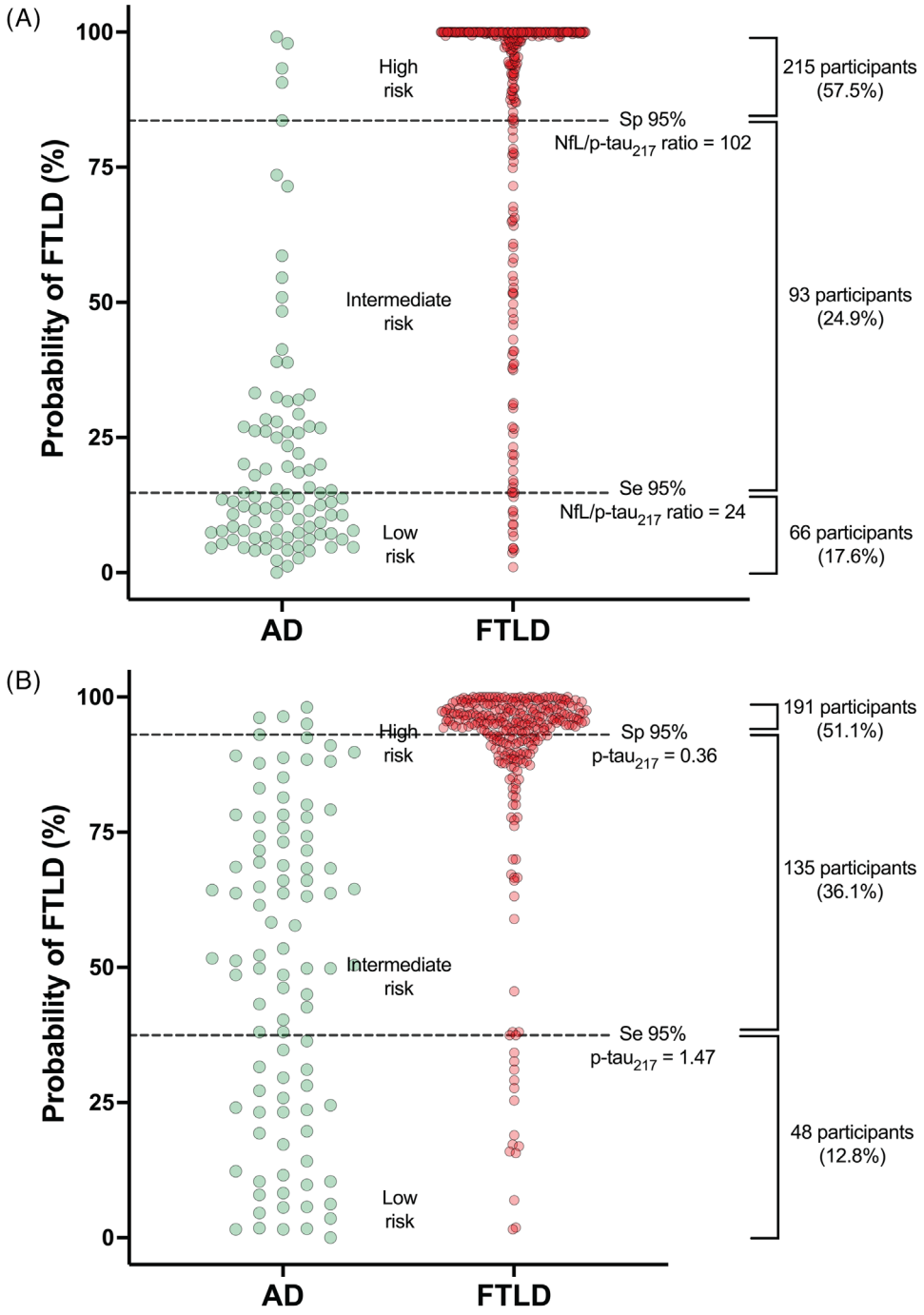

FIGURE 4 Risk stratification with a plasma NfL/p-tau$_{217}$ ratio and a p-tau$_{217}$-based models. Distribution of predicted probabilities of FTLD diagnosis based on a logistic regression model including the NfL/p-tau$_{217}$ ratio (A) and p-tau$_{217}$ (B) as predictor. The NfL/p-tau$_{217}$ ratio and the p-tau$_{217}$ values corresponding to the evaluated risk thresholds are demonstrated and accompanied by the metric used to define them (95% Se and 95% Sp). The lower dashed line demonstrates where the 95% sensitivity low-risk threshold falls on the probability distribution, with the upper line corresponding to the 95% specificity high-risk threshold. AD, Alzheimer's disease; FTLD, frontotemporal lobar degeneration associated syndromes; NfL, neurofilament light chain; p-tau, phosphorylated tau; Se, sensitivity; Sp, specificity.

may be due to peripheral compartments, such as platelets and exosomes, releasing A$\beta_{1\text{-}42}$ into the plasma, or increased blood–brain barrier permeability in AD allowing greater leakage.[49,50] Interestingly, one study reported higher levels of A$\beta_{1\text{-}42}$ in AD compared to FTD,[51] while two others did not.[52,53]

One of the key strengths of this study is its focus on the differential diagnosis between AD and FTLD, two of the most common causes of early-onset dementia, by using a large cohort and comprehensively evaluating the entire spectrum of FTLD-associated syndromes. By assessing a broad panel of biomarkers within a single cohort,

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this research provides valuable insights into the relative accuracy of each marker and its potential utility in clinical practice. Accurately distinguishing between AD and FTLD with these biomarkers could significantly reduce the need for invasive and costly procedures, such as CSF sampling or amyloid PET imaging. Our application of a three-range approach, as recommended by the Alzheimer's Association[54] and recently proposed by Brum et al.[55] and et al.,[11] demonstrated that using thresholds corresponding to 95% sensitivity and specificity could reduce CSF testing by ≈ 75%, while more stringent thresholds of 97.5% reduced the need for CSF testing by 54%. This strategy optimizes resource use and ensures that patients with uncertain biomarker profiles receive the appropriate follow-up.[54,55]

The findings of this study align with the recommendations of the Global CEO Initiative on AD blood-based biomarkers working group, which advocates for blood-based biomarkers to be used as triaging tests before confirmatory tests like amyloid PET or CSF analysis.[26] According to the group, a blood-based biomarker test should have a sensitivity of ≥90% and a specificity of ≥ 85% in primary care, and ≥ 75% to 85% specificity in secondary care, depending on the availability of follow-up testing.[26] The sensitivity and specificity of the NfL/p-tau$_{217}$ ratio identified in this study are within these recommended ranges, suggesting that this ratio could be a valuable tool in both primary and secondary care settings for the initial assessment of patients with suspected neurodegenerative disease.

While the findings of this study are promising, there are several limitations that should be acknowledged. One significant limitation is the lack of autopsy-proven diagnoses, which is considered the gold standard for confirming neurodegenerative diseases. However, the majority of participants did undergo CSF analysis or amyloid PET imaging, which provides a very high level of diagnostic confidence and is in line with the appropriate use recommendations of the Alzheimer's Association to determine clinical robustness.[54] Another limitation is the lack of longitudinal data, which restricts the ability to assess the utility of these biomarkers over time or their potential role in monitoring disease progression, as has been shown for GFAP or NfL.[56] The monocentric design may limit the generalizability of the findings, which could be improved by multi-center studies with larger and more diverse populations. Additionally, the retrospective design may introduce selection bias and limit control over confounding factors, highlighting the need for prospective studies to confirm these findings and further explore the clinical utility of these plasma biomarkers.

In conclusion, this study, which simultaneously evaluated a broad range of dementia-related biomarkers in a large cohort of patients, supports the use of plasma p-tau$_{217}$ and the NfL/p-tau$_{217}$ ratio as non-invasive biomarkers for differentiating AD from FTLD, offering a promising alternative to traditional methods for early diagnosis and treatment guidance. The p-tau$_{217}$/NfL ratio offers slightly enhanced diagnostic accuracy, but the marginal difference in specificity compared to p-tau$_{217}$ alone indicates that both biomarkers have complementary strengths, depending on clinical requirements. Further research is needed to address the study's limitations and fully explore the potential of these biomarkers in neurodegenerative disease management.

AUTHOR CONTRIBUTIONS

Alberto Benussi and Barbara Borroni contributed to the conception and design of the study; Alberto Benussi, Hanna Huber, Kübra Tan, Valentina Cantoni, Jasmine Rivolta, Maria Sofia Cotelli, Andrea L. Benedet, Kaj Blennow, Henrik Zetterberg, Nicholas J. Ashton, and Barbara Borroni contributed to the acquisition and analysis of data; Alberto Benussi and Barbara Borroni contributed to drafting the text or preparing the figures.

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CONFLICT OF INTEREST STATEMENT

H.Z. has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, LabCorp, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, Roche, and WebMD;and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). B.B. has served on scientific advisory boards for Alector, Alexion/Astrazeneca, AviadoBio, Lilly, Denali, Wave, and UCB. The other authors have nothing to disclose.

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CONSENT STATEMENT

Full written informed consent was obtained from all subjects according to the Declaration of Helsinki. The Brescia Ethics Committee approved the study protocol.

ORCID

Alberto Benussi https://orcid.org/0000-0002-8703-6940

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SUPPORTING INFORMATION

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

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