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SHORT REPORT

A comparison of p-tau assays for the specificity to detect tau changes in Alzheimer's disease

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Abstract

INTRODUCTION: We evaluated differences in p-tau levels between Alzheimer's disease (AD), a condition with brain-specific changes in p-tau, and amyotrophic lateral sclerosis (ALS), a condition associated with increases in peripheral p-tau levels.

METHODS: Cerebrospinal fluid and plasma from 668 participants were analyzed using immunoassays specific for the low-molecular-weight (LMW) tau isoforms present in the brain (i.e., p-tau217$_{Lilly}$, p-tau181$_{Lilly}$) and those that detect both LMW- and

high-molecular-weight (HMW) tau expressed in the peripheral nervous system (i.e., p-tau217$_{AlzPath}$, p-tau181$_{UGOT}$).

RESULTS: Increases in plasma p-tau in ALS versus controls were significantly smaller for the LMW-specific p-tau assays (15.9%–20.5%) compared with non-specific assays (92.0%–121.3%). The LMW-specific p-tau assays showed significantly larger plasma p-tau increases in AD versus ALS, discriminating AD from ALS with areas under the curve (AUCs; 0.890.93) higher than the AUCs of the non-specific assays (0.54–0.74).

DISCUSSION: LMW-specific p-tau assays could be more useful in the diagnostic workup of AD, especially in population-based communities where conditions causing peripheral neuropathy are frequent.

KEYWORDS
Alzheimer's disease, amyotrophic lateral sclerosis, biomarker, blood, low-molecular-weight tau, p-tau

Highlights

- Increases in plasma phosphorylated tau (p-tau) in amyotrophic lateral sclerosis (ALS) versus controls were significantly smaller for low-molecular-weight (LMW)–specific p-tau assays (i.e., p-tau217Lilly, p-tau181Lilly) compared with p-tau assays that also detect high-molecular-weight (HMW) assays (i.e., p-tau217AlzPath, p-tau181UGOT).
- The LMW-specific p-tau assays showed significantly larger increases in plasma p-tau in AD versus ALS compared with the non-specific assays.
- The LMW-specific p-tau assays discriminated AD from ALS with higher precision, showing significantly better performance than the non-specific assays.
- LMW-specific p-tau assays could be more useful in the diagnostic workup of AD, especially in population-based communities where conditions causing peripheral neuropathy (such as ALS) are frequent.

1 | BACKGROUND

Cerebrospinal fluid (CSF) tests for amyloid beta (Aβ) peptides (Aβ_{42} and Aβ_{40}) and phosphorylated tau-181 (p-tau181) have been used for several decades as biomarkers of Alzheimer's disease (AD).[1] More recently, CSF p-tau181/Aβ_{42} and Aβ_{42}/Aβ_{40} were approved by the U.S. Food and Drug Administration (FDA) to diagnose AD.[2–4] Furthermore, during the past 4 years, blood-based p-tau biomarkers of AD (and p-tau217, in particular) have been applied extensively in research settings and clinical trials, and those showing minimum acceptable performance are soon expected to receive regulatory approval for implementation in clinical practice.[5–7] It is important to note that certain p-tau217 assays have performance comparable to clinically used CSF tests, reliably detecting AD even in real-world primary care settings.[8,9] These breakthroughs have changed the diagnostic landscape for patients with AD.

Increased levels of p-tau217 and p-tau181 in CSF and plasma reflect AD-related brain Aβ and tau pathologies, whereas most other neurodegenerative disease affecting the central nervous system (CNS), including non-AD primary tauopathies, do not clearly influence concentrations of these biomarkers.[1] However, recent studies have reported elevated blood plasma or serum levels of p-tau181[10,11] and p-tau217[12] in patients with amyotrophic lateral sclerosis (ALS) compared to healthy controls. In these studies, p-tau concentrations in blood were associated with lower motor neuron dysfunction. Furthermore, increased immunoreactivity for both p-tau variants was detected in muscle biopsies from ALS patients, suggesting that the increase in blood p-tau181 and p-tau217 in ALS may be from degenerating peripheral nerves and denervated muscle fibers.[10–12] Of interest, tau expressed in the peripheral nervous system (PNS) is a high-molecular-weight (HMW, 110 kDa) isoform, whereas six low-molecular-weight (LMW, 37–46 kDa) isoforms are predominant in the CNS where exon 4a of the microtubule-associated protein tau (*MAPT*) gene is not transcribed.[13,14]

Currently available immunoassays for quantitation of the CSF and blood levels of various p-tau variants differ in their specificity for

LMW and HMW tau (eFigure 1). For example, the detection antibody in the p-tau assays designed by Lilly Research Laboratories ($p\text{-tau217}_{Lilly}$ and $p\text{-tau181}_{Lilly}$) targets the amino acid (aa) 111–130 region, which is present only in the LMW tau isoforms expressed in the CNS.[15–17] On the other hand, p-tau assays used in the previous studies on ALS, ALZpath p-tau217 ($p\text{-tau217}_{ALZpath}$) and p-tau181 from University of Gothenburg ($p\text{-tau181}_{UGOT}$),[10–12] as well as several other p-tau assays include a detection antibody recognizing the N-terminal epitope (aa 6–18) expressed in both CNS and PNS tau.[18–20] Of note, capture antibodies in these p-tau assays are specific for the corresponding phospho-epitopes. Another assay selectively measuring brain-derived total tau (BD-tau), that works as an indicator of neurodegeneration intensity in AD, utilizes a capture antibody binding to LMW but not HMW tau isoforms and detection antibody raised against the N-terminal region, which is not specific for a particular phosphorylation variant.[21] We hypothesized that assays not specific for LMW p-tau present in the CNS would detect higher concentrations of p-tau in plasma (but not CSF[10]) of patients with peripheral nerve damage. To test this, we analyzed paired plasma and CSF samples from patients with ALS (a disease with combined degeneration of upper and lower motor neurons and their associated tracts in the CNS and PNS) and AD (a condition where neurodegeneration is restricted to the CNS) as well as control individuals using immunoassays that (1) preferentially detect tau expressed in the brain, that is, $p\text{-tau217}_{Lilly}$, $p\text{-tau181}_{Lilly}$, BD-tau, or (2) do not differentiate between brain-derived and peripheral p-tau, that is, $p\text{-tau217}_{ALZpath}$ and $p\text{-tau181}_{UGOT}$.

RESEARCH-IN-CONTEXT

1. **Systematic review**: The authors performed a literature search using PubMed and reviewed relevant publications. Recent evidence suggests that blood concentrations of Alzheimer's disease (AD) biomarker, phosphorylated-tau (p-tau), might be increased in conditions associated with peripheral nerve damage such as amyotrophic lateral sclerosis (ALS).
2. **Interpretation**: Our findings indicate that p-tau assays detecting only low-molecular-weight (LMW) tau present in the brain show larger plasma p-tau increases in AD versus ALS and discriminate AD from ALS with higher precision compared with p-tau assays that also detect high-molecular-weight tau expressed in the peripheral nervous system.
3. **Future directions**: LMW-specific p-tau assays are preferable in the diagnostic workup of AD, with fewer false positive findings, especially in diverse population-based communities where peripheral neuropathy may produce high p-tau levels when using non–LMW-specific assays.

2 | METHODS

2.1 | Participants

The study comprised control individuals and patients with ALS and AD from three cohorts. Participants in Cohort 1 were referred to the Department of Neurology, Umeå University Hospital, Sweden with suspicion of having ALS and evaluated according to the European Federation of Neurological Societies diagnostic algorithm for managing ALS.[22] The ALS group included 321 patients, of whom 309 were diagnosed with ALS and 12 with other motor neuron diseases. The control group included 11 healthy individuals and 34 patients with non-motor neuron disease diagnoses. In Cohort 2 from the Institute of Neurological Sciences of Bologna, 139 participants had ALS according to the Revised El Escorial criteria[23] and 59 were healthy controls. Cohort 3 included 56 neurologically healthy controls and 48 patients with AD (10 with mild cognitive impairment [MCI] due to AD, 38 with AD dementia) from the Swedish BioFINDER-2 study.[16] The MCI classification was operationalized as performing worse than −1.5 z-scores in any cognitive domain according to a regression-based norms, accounting for age and education and the test performance in Aβ-negative controls.[24] AD dementia was diagnosed based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and AD was further confirmed with Aβ biomarkers based on the National Institute on Again–Alzheimer's Association (NIA-AA) criteria for AD.[25]

2.2 | Plasma and CSF analysis

CSF and blood plasma were collected at the same visit using standard procedures. Samples were aliquoted shortly after collection and stored at −80°C until analysis. In Cohort 2, lumbar puncture and CSF collection was only performed in patients with ALS. CSF and plasma samples were analyzed using the p-tau217 and p-tau181 immunoassays developed by Lilly Research Laboratories, commercially available the Single molecule Array (Simoa) ALZpath p-tau217 and neurofilament light (NfL) immunoassays (Quanterix), and in-house Simoa p-tau181 and BD-tau immunoassays developed by University of Gothenburg as described previously.[18,21,26] Samples from the different cohorts were distributed evenly between the runs.

2.3 | Statistical analysis

R version 4.4.0[27] was used for statistical analysis. Biomarker data were skewed and were therefore log10-transformed before statistical analyses, if not stated otherwise. Group differences were assessed using univariate linear regression models with biomarker values as dependent variables and diagnosis and age as independent variables. For each biomarker, we also determined the percent group difference in the median plasma biomarker concentration (untransformed) with the following equation:

$$\frac{median_{group2} - median_{group1}}{median_{group1}} * 100$$

TABLE 1 Participant characteristics.

	Controls	Amyotrophic lateral sclerosis	Alzheimer's disease
N	160	460	48
Age, years	63.0 (56.0–77.5)	65.1 (56.3–71.8)	74.0 (69.8–78.0)
Sex, male/female, *N* (%)	85 (53.1%) / 75 (46.9%)	273 (59.3%) / 187 (40.7%)	30 (62.5%) / 18 (37.5%)
CSF			
p-tau217$_{Lilly}$ (pg/mL) *LMW specific*	8.3 (6.4–11.5) *N* = 97	7.5 (5.4–10.6) *N* = 459	77.4 (52.7–100.1) *N* = 48
p-tau181$_{Lilly}$ (pg/mL) *LMW specific*	36.2 (27.4–47.7) *N* = 97	30.3 (22.7–40.6) *N* = 459	125.2 (90.8–162.5) *N* = 48
BD-tau (pg/mL) *LMW specific*	198.2 (149.7–290.1) *N* = 97	224.2 (162.3–302.5) *N* = 460	426.6 (301.5–522.9) *N* = 48
p-tau217$_{ALZpath}$ (pg/mL) *non–LMW specific*	8.8 (6.2–14.5) *N* = 97	8.6 (5.7–13.9) *N* = 460	65.5 (50.9–88.9) *N* = 48
p-tau181$_{UGOT}$ (pg/mL) *non–LMW specific*	101.1 (80.2–114.0) *N* = 97	96.1 (79.4-+117.6) *N* = 460	242.2 (194.7–287.9) *N* = 48
Plasma			
p-tau217$_{Lilly}$ (pg/mL) *LMW specific*	0.252 (0.196–0.322) *N* = 155	0.303 (0.235–0.385) *N* = 459	0.754 (0.573–0.927) *N* = 48
p-tau181$_{Lilly}$ (pg/mL) *LMW specific*	2.1 (1.8–2.6) *N* = 155	2.4 (2.0–3.0) *N* = 459	4.5 (3.8–5.8) *N* = 48
BD-tau (pg/mL) *LMW specific*	3.4 (2.7–4.2) *N* = 154	3.7 (2.8–4.9) *N* = 446	4.8 (3.6–5.4) *N* = 48
p-tau217$_{ALZpath}$ (pg/mL) *non–LMW specific*	0.330 (0.253–0.441) *N* = 149	0.731 (0.420–1.232) *N* = 451	1.2 (1.0-1.7) *N* = 48
p-tau181$_{UGOT}$ (pg/mL) *non–LMW specific*	6.8 (5.4–9.2) *N* = 155	13.1 (8.7–23.3) *N* = 459	12.7 (9.5–15.1) *N* = 48

Note: Data are shown as median (interquartile range) unless otherwise specified.
Abbreviations: BD-tau, brain-derived total tau; CSF, cerebrospinal fluid; LMW, low-molecular-weight; p-tau, phosphorylated tau.

Between-biomarker differences in the percent group differences were estimated using bootstrapping. Discriminative accuracies of biomarkers were assessed with the receiver-operating characteristic (ROC) curve analysis; areas under the curve (AUCs) of the two ROC curves were compared using the DeLong test. *p*-values were adjusted for multiple comparisons using the Bonferroni test or false discovery rate, as indicated in the figure legends and table footnotes. Two-sided $p < 0.05$ was considered statistically significant.

3 | RESULTS

The study included 160 controls, 460 patients with ALS, and 48 patients with AD (Table 1). Patients with AD were, on average, older than controls and patients with ALS, whereas sex distribution was balanced across the groups.

3.1 | p-tau biomarker levels in CSF

There were significant differences in CSF levels of all examined biomarkers across the three diagnostic groups (eTable 1). Post hoc analysis (Figure 1A-1E, eTable 2) revealed that CSF concentrations of p-tau217$_{Lilly}$, p-tau217$_{ALZpath}$, and p-tau181$_{UGOT}$ did not differ between controls and ALS, whereas p-tau181$_{Lilly}$ levels were somewhat lower in ALS. At the same time, higher CSF concentrations of all biomarkers were seen in AD compared with both controls and ALS. All CSF p-tau assays distinguished with high accuracy AD from ALS (AUC [95% confidence interval (CI)], 0.968–0.985 [0.952–0.983 to 0.977–0.994]) (Figure 1F, Table 2).

3.2 | P-tau biomarker levels in plasma

In contrast to the CSF results, plasma levels of p-tau217$_{Lilly}$, p-tau217$_{ALZpath}$, p-tau181$_{Lilly}$, and p-tau181$_{UGOT}$ were higher in both ALS and AD than in controls (Figure 2, eTable 2). However, the increase in ALS relative to controls was significantly smaller for the LMW-specific p-tau217 assay (Lilly: 20.5% increase) than the non–LMW-specific p-tau217 assay (ALZpath: 121.3% increase, $p_{diff} < .001$). Similarly, the LMW-specific p-tau181 assay exhibited a significantly lower increase in ALS versus controls (Lilly: 15.9%) than the non–LMW-specific p-tau181 assay (UGOT: 92.0%, $p_{diff} < .001$).

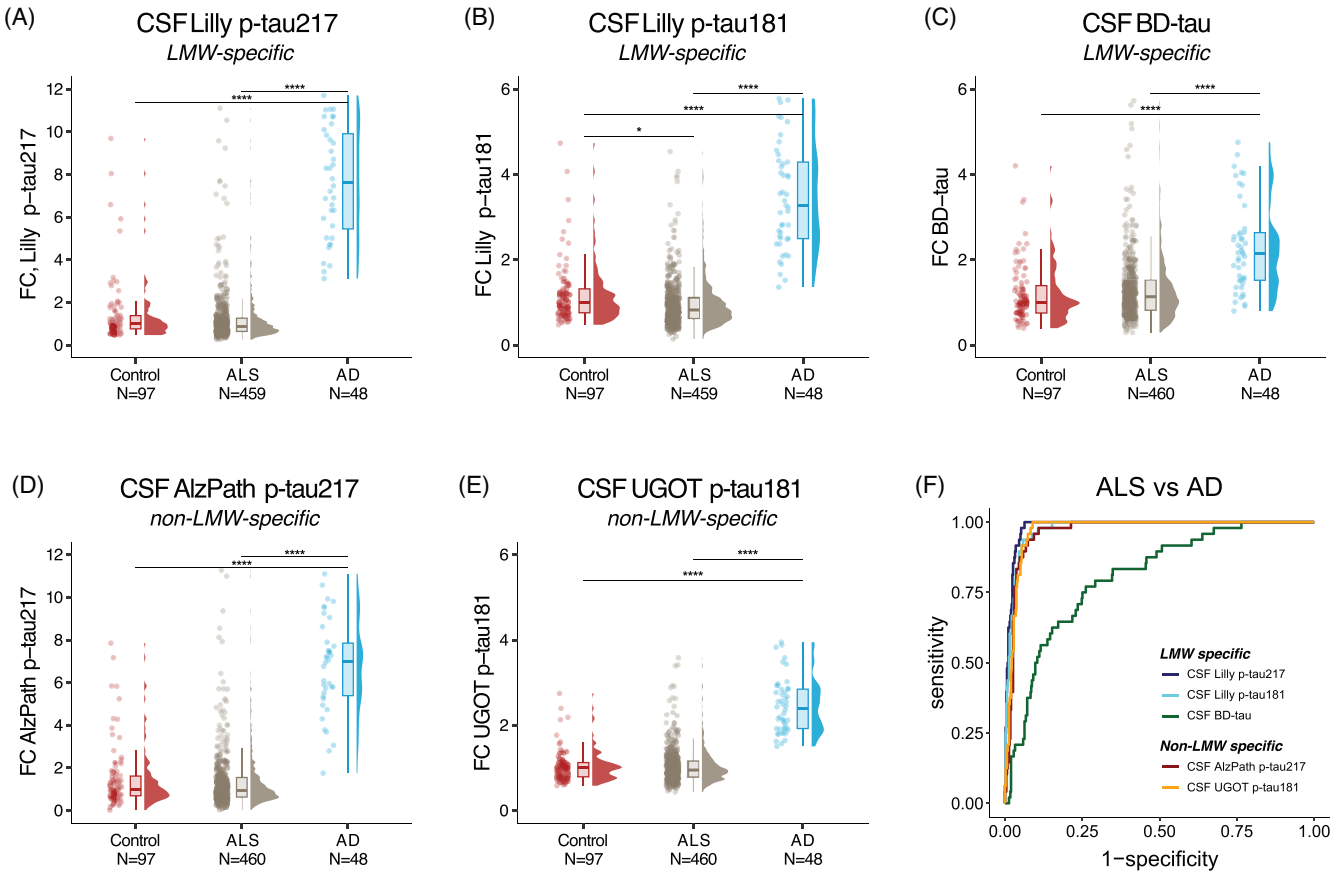

FIGURE 1 Cerebrospinal fluid (CSF) biomarker levels across diagnostic groups. Fold increases in CSF levels of Lilly phosphorylated tau (p-tau)217 (**A**), Lilly p-tau181 (**B**), brain-derived tau (BD-tau, **C**), ALZpath p-tau217 (**D**), and UGOT p-tau181 (**E**) in patients with Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS) and control participants. Several outliers (Lilly p-tau217, $n = 13$; ALZpath p-tau217, $n = 17$; Lilly p-tau181, $n = 5$; BD-tau, $n = 3$) are not shown but were included in the statistical analysis. *p*-values, adjusted for multiple comparison using the Bonferroni test (three comparisons per individual biomarker), are from the analysis of variance with log-transformed biomarkers as dependent variables and diagnosis as independent variable adjusting for age. (**F**) Receiver-operating characteristic for differentiating ALS from AD. FC, fold change; LMW, low-molecular-weight; UGOT, University of Gothenburg.

In addition, we found that the levels of p-tau217$_{Lilly}$, p-tau217$_{ALZpath}$, and p-tau181$_{Lilly}$, but not p-tau181$_{UGOT}$, were higher in AD than in ALS (Figure 2, eTable 2). However, the difference between the ALS and AD groups was significantly larger for the LMW-specific p-tau217 assay (Lilly: 148.6% increase) than the non–LMW-specific p-tau217 assay (ALZpath: 69.9% increase, $p_{diff} < .001$). Likewise, the LMW-specific p-tau181 assay exhibited a significantly larger change in AD versus ALS (Lilly: 86.5% increase) than the non–LMW-specific p-tau181 assay (UGOT; 3.7% decrease; $p_{diff} < .001$). In line with these results, the LMW-specific plasma p-tau217$_{Lilly}$ (AUC [95% CI], 0.934 [0.908–0.961]) and p-tau181$_{Lilly}$ (AUC [95% CI], 0.889 [0.846–0.932]) assays accurately discriminated AD from ALS, with significantly higher AUCs than the non–LMW-specific p-tau217$_{ALZpath}$ (AUC [95% CI], 0.741 [0.678–0.804]; $p_{diff} < .001$) and p-tau181$_{UGOT}$ (AUC [95% CI], 0.543 [0.476–0.61]; $p_{diff} < 0.001$) assays (Figure 2F, Table 2). Correlations between plasma and CSF concentrations of the biomarkers are shown in eFigure 2.

3.3 | CSF and plasma neurodegeneration biomarkers

Similar to the LMW-specific p-tau (p-tau217$_{Lilly}$ and p-tau181$_{Lilly}$), BD-tau showed lower increases in ALS versus controls in plasma (7.3%) (Figure 2C) but separated AD from ALS with lower accuracy (AUC [95% CI], 0.651 [0.583–0.720]; $p_{diff} < .001$) than the LMW-specific p-tau assays (Figure 2F).

In contrast to the tau differences, both CSF and plasma levels of NfL were, as expected,[28] significantly and markedly higher in ALS compared to both controls and AD (eFigure 3).

3.4 | Sensitivity analyses

To ensure that the lack of CSF in control individuals from Cohort 2 did not bias our findings, we performed a sensitivity analysis including only

TABLE 2 Diagnostic accuracies of cerebrospinal fluid (CSF) and plasma biomarkers.

	ALS vs AD		CN vs ALS		CN vs AD	
Biomarker	***AUC (95% CI)***	***p-value***	***AUC (95% CI)***	***p-value***	***AUC (95% CI)***	***p-value***
CSF						
p-tau217$_{Lilly}$ *LMW specific*	0.985 (0.977–0.994)	Reference	0.560 (0.499–0.621)	Reference	0.983 (0.966–1.00)	Reference
p-tau181$_{Lilly}$ *LMW specific*	0.977 (0.965–0.989)	**0.009**	0.619 (0.561–0.678)	**1.3e-07**	0.96 (0.931–0.988)	**0.009**
BD-tau *LMW specific*	0.807 (0.747–0.867)	**4.0e-09**	0.545 (0.481–0.608)	0.85	0.831 (0.764–0.898)	**4.4e-06**
p-tau217$_{AlzPath}$ *non–LMW specific*	0.968 (0.952–0.983)	**0.002**	0.518 (0.455–0.582)	**0.049**	0.966 (0.939–0.992)	0.06
p-tau181$_{UGOT}$ *non–LMW specific*	0.972 (0.96–0.985)	**1.9e-04**	0.517 (0.455–0.579)	**0.016**	0.977 (0.955–0.999)	0.16
Plasma						
p-tau217$_{Lilly}$ *LMW specific*	0.934 (0.908–0.961)	Reference	0.631 (0.579–0.683)	Reference	0.970 (0.948–0.991)	Reference
p-tau181$_{Lilly}$ *LMW specific*	0.889 (0.846–0.932)	**0.0002**	0.624 (0.572–0.676)	0.75	0.943 (0.911–0.976)	**0.021**
BD-tau *LMW specific*	0.651 (0.583–0.72)	**1.3e-18**	0.563 (0.512–0.614)	**0.044**	0.739 (0.66–0.817)	**1.9e-08**
p-tau217$_{AlzPath}$ *non–LMW specific*	0.741 (0.678–0.804)	**1.1e-11**	0.797 (0.757–0.836)	**8.7e-08**	0.942 (0.897–0.987)	0.30
p-tau181$_{UGOT}$ *non–LMW specific*	0.543 (0.476–0.61)	**5.9e-20**	0.787 (0.747–0.827)	**1.1e-06**	0.833 (0.77–0.896)	**1.2e-05**

Note: Area under the curve (AUC) and 95% confidence interval (CI) are from receiver-operating characteristic (ROC) curve analysis. AUCs were compared with the DeLong test. *p*-values were adjusted for multiple comparisons using false discovery rate.
Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BD-tau brain-derived total tau; CN, control; LMW, low-molecular-weight; p-tau, phosphorylated tau.

participants from Cohort 1 and Cohort 3, which revealed very similar results. Specifically, none of the CSF p-tau biomarkers was increased in ALS compared with controls, whereas all CSF p-tau biomarkers were elevated in AD compared with ALS (eTables 3-4), distinguishing with high accuracy these two groups (AUC [95% CI], 0.961–0.980 [0.942–0.980 to 0.968–0.992]).

4 | DISCUSSION

We found that increases in plasma p-tau217 and p-tau181, measured using the LMW-specific assays, were significantly less pronounced in ALS relative to controls than when using assays that do not differentiate between brain-derived LMW and peripheral HMW tau. Furthermore, the LMW-specific plasma assays showed larger increases in AD and discriminated AD from ALS with higher accuracies (AUC$_{range}$, 0.89–0.93) than the non–LMW-specific assays (AUC$_{range}$, 0.54–0.74). In contrast, CSF levels of p-tau biomarkers were not increased in ALS compared with controls. All four CSF p-tau assays had high performance for differentiating AD from ALS (AUC$_{range}$, 0.97–0.98). Similar to the LMW-specific p-tau assays, the LMW-specific BD-tau also exhibited a smaller increase in ALS versus controls in plasma. However, it separated AD from ALS with lower accuracy (AUC$_{range}$, 0.54–0.74) than the LMW-specific p-tau assays, likely because phosphorylation status (and tau pathology) is better at differentiating AD and ALS, whereas non-phosphorylated brain-derived assays are mostly associated with neurodegeneration intensity and severity.[21]

Our results on the non-LMW specific assays are consistent with previous reports that p-tau181 and p-tau217 levels, measured with the Quanterix Simoa assay, which detects both LMW and HMW tau, were elevated in blood of ALS and AD patients, poorly discriminating between AD and ALS.[10–12] It is important to note that one key finding of the present study is that plasma p-tau biomarkers analyzed with the LMW-specific assays were less affected in ALS and could separate AD from ALS with high accuracy. Moreover, we did not observe increases in CSF levels of any of the tau biomarkers in ALS versus controls (which is in line with prior literature[29]) indicating that hyperphosphorylation of tau in ALS does not occur in the CNS. Collectively, these data suggest that ALS, a condition with mixed central and peripheral neurodegeneration, leads to increased release of HMW p-tau, which probably originates from the degenerating lower motor axons and atrophic muscle fibers.

This explorative study is not without limitations. First, CSF was not obtained from all control participants. Nevertheless, the sample size of the control group with available CSF was relatively large. Second, we cannot rule out that some of the ALS patients had incipient

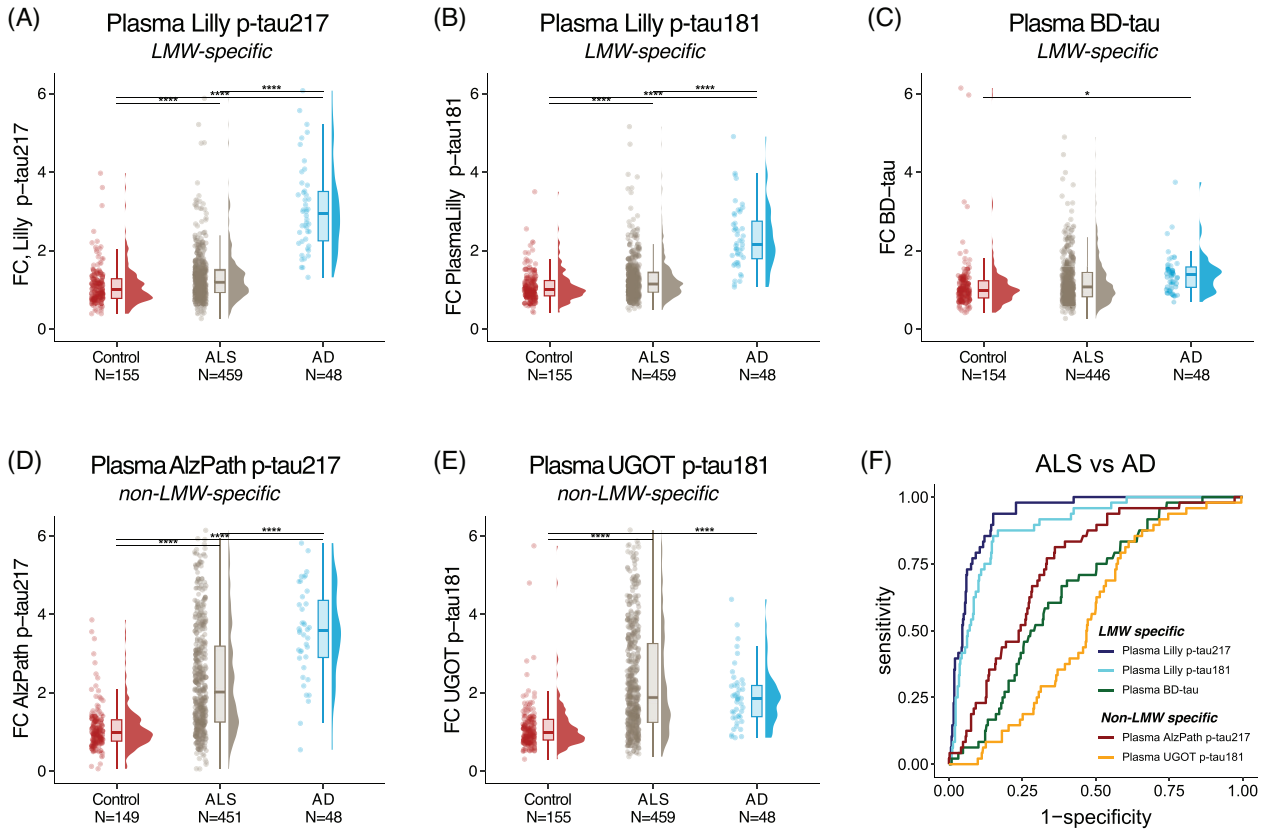

FIGURE 2 Plasma biomarker levels across diagnostic groups. Fold increases in plasma levels of Lilly phospho-tau (p-tau)217 (**A**), Lilly p-tau181 (**B**), brain-derived tau (BD-tau, **C**), ALZpath p-tau217 (**D**), and UGOT p-tau181 (**E**) in patients with Alzheimer's Disease (AD) and amyotrophic lateral sclerosis (ALS) and control participants. Several outliers (Lilly p-tau217, $n = 5$; ALZpath p-tau217, $n = 47$; Lilly p-tau181, $n = 2$; UGOT p-tau181, $n = 18$; BD-tau, $n = 2$) are not shown but were included in the statistical analysis. *p*-values, adjusted for multiple comparison using the Bonferroni method (three comparisons per individual biomarker), are from the analysis of variance with log-transformed biomarkers as dependent variables and diagnosis as independent variable adjusting for age. (**F**) Receiver operating characteristic for differentiating ALS from AD. FC, fold change; LMW, low-molecular weight; UGOT, University of Gothenburg.

AD. Therefore, future studies should include participants with established CSF Aβ42/40 or Aβ-PET (positron emission tomography) status or where post-mortem CNS autopsy tissue is available. Third, we only studied AD and ALS; further work is needed to understand whether our findings in ALS extend to other diseases with peripheral neurodegeneration such as spinal-bulbar muscular atrophy, diabetic neuropathy, or Guillain-Barré syndrome.

In conclusion, plasma concentrations of LMW p-tau isoforms were influenced to a much lesser extent by peripheral neurodegeneration than by AD-related brain pathology. Plasma assays specific for LMW p-tau are preferable in the diagnostic workup of AD, with fewer false-positive findings, especially in diverse population-based communities where peripheral neuropathy may produce high p-tau levels when using non–LMW-specific assays.

AUTHOR CONTRIBUTIONS

All authors collected the data and reviewed the manuscript for intellectual content. Shorena Janelidze and Oskar Hansson analyzed and interpreted the data, prepared figures, and cowrote the manuscript. Oskar Hansson was the principal designer and coordinator of the study and overviewed collection, analysis, and interpretation of the study data.

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CONFLICT OF INTEREST STATEMENT

K.B. has served as a consultant and at advisory boards for Abbvie, AC Immune, ALZpath, AriBio, Beckman-Coulter, BioArctic, Biogen, Eisai, Lilly, Moleac Pte. Ltd, Neurimmune, Novartis, Ono Pharma, Prothena, Quanterix, Roche Diagnostics, Sanofi, and Siemens Healthineers; has served on data-monitoring committees for Julius Clinical and Novartis; has given lectures, produced educational materials, and participated in educational programs for AC Immune, Biogen, Celdara Medical, Eisai, and Roche Diagnostics; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper. H.Z. has served at 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, Quanterix, 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). O.H. is a part-time employee of Eli Lilly, and he has previously acquired research support (for Lund University) from AVID Radiopharmaceuticals, Biogen, C2N Diagnostics, Eli Lilly, Eisai, Fujirebio, GE Healthcare, and Roche. In the past 2 years, he has received consultancy/speaker fees from ALZpath, BioArctic, Biogen, Bristol Meyer Squibb, Eisai, Eli Lilly, Fujirebio, Merck, Novartis, Novo Nordisk, Roche, Sanofi, and Siemens. N.M.C. has received consultancy/speaker fees from Biogen, Owkin, and Merck.

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CONSENT STATEMENT

All studies were approved by the regional ethics committees (the Regional Ethics Committee, Lund, Sweden; the ethics committee of "Area Vasta Emilia Centro", Bologna, Italy; the Medical Ethical Committee, Umeå, Sweden). Participants provided written informed consent to participate in the study.

DATA AVAILABILITY STATEMENT

Anonymized data for the BioFINDER partitipants included in this study (PI: OH) will be shared by request from a qualified academic investigator for the sole purpose of replicating procedures and results presented in the article and as long as data transfer is in agreement with EU legislation on the general data protection regulation and decisions by the Ethical Review Board of Sweden and Region Skåne, which should be regulated in a material transfer agreement.

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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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