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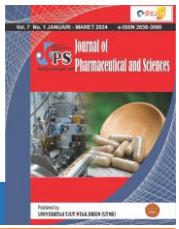

Plasma pTau181 and Neuropsychiatric Symptoms in Alzheimer's Dementia: Insights from a Cross-Sectional Study

Plasma pTau181 dan Gejala Neuropsikiatri pada Demensia Alzheimer: Sebuah Studi Cross-Sectional

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Abstract

Alzheimer's disease is the leading cause of dementia, marked by progressive cognitive decline and neuropsychiatric disturbances collectively known as behavioral and psychological symptoms of dementia (BPSD). Plasma phosphorylated tau at threonine-181 (pTau181) has emerged as a minimally invasive biomarker of tau-related neurodegeneration, but its association with BPSD remains uncertain. This study investigated the relationship between plasma pTau181 levels and BPSD in Alzheimer's dementia. An analytical observational study with a cross-sectional design was conducted in patients clinically diagnosed with predefined eligibility criteria. Plasma pTau181 concentrations were measured using enzyme-linked immunosorbent assay (ELISA), while BPSD was assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q). Statistical analyses were performed to examine associations between plasma pTau181 and BPSD status. Plasma pTau181 levels ranged from 4.32 to 97.23 pg/mL, with a median plasma pTau181 level of 19.29 pg/mL (IQR: 11.81-25.05) in patients without BPSD and 20.67 pg/mL (IQR: 11.81-43.41) in those with BPSD. No significant differences in pTau181 levels were observed between patients with and without BPSD (p = 0.310). These findings suggest that plasma pTau181 may not be directly related to the presence of BPSD in Alzheimer's dementia. While plasma pTau181 remains a promising biomarker of tau pathology, its predictive value for neuropsychiatric symptoms appears limited. Longitudinal studies are needed to explore its role in BPSD pathophysiology further.

***Keywords*: Alzheimer's dementia; Behavioral and psychological symptoms of dementia; Neuropsychiatry; NPI-Q; p-Tau181 plasma.**

Abstrak

Penyakit Alzheimer adalah penyebab utama demensia, yang ditandai dengan penurunan kognitif yang progresif dan gangguan neuropsikiatri yang dikenal sebagai *behavioral and psychological symptoms of dementia* (BPSD). Plasma terfosforilasi tau pada treonin-181 (pTau181) telah dikenal sebagai biomarker invasif minimal untuk penyakit neurodegenerasi terkait tau, tetapi hubungannya dengan BPSD masih belum pasti. Penelitian ini menyelidiki hubungan antara kadar pTau181 plasma dan BPSD pada demensia Alzheimer. Penelitian observasional analitik dengan desain cross-sectional ini dilakukan pada pasien yang didiagnosis secara klinis yang memenuhi kriteria kelayakan yang telah ditentukan. Konsentrasi pTau181 plasma diukur dengan menggunakan *enzyme-linked immunosorbent assay* (ELISA), sedangkan BPSD dinilai dengan menggunakan *Neuropsychiatric Inventory Questionnaire* (NPI-Q). Analisis statistik dilakukan untuk memeriksa hubungan antara pTau181 plasma dan status BPSD. Kadar pTau181 plasma berkisar antara 4,32 hingga 97,23 pg / mL, dengan kadar pTau181 plasma rata-rata adalah 19,29 pg / mL (IQR: 11,81-25,05) pada pasien tanpa BPSD dan 20,67 pg / mL (IQR: 11,81 - 43,41) pada pasien dengan BPSD. Tidak ada perbedaan signifikan dalam kadar pTau181 yang diamati antara pasien dengan dan tanpa BPSD (p = 0,310). Temuan ini menunjukkan bahwa

pTau181 plasma mungkin tidak secara langsung terkait dengan keberadaan BPSD pada demensia Alzheimer. Meskipun pTau181 plasma tetap menjadi biomarker yang menjanjikan untuk patologi tau, nilai prediktifnya untuk gejala neuropsikiatri tampaknya terbatas. Studi longitudinal diperlukan untuk mengeksplorasi lebih lanjut perannya dalam patofisiologi BPSD.

Kata Kunci: Demensia Alzheimer; BPSD; Neuropsikiatri; NPI-Q; plasma p-Tau181.

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Introduction

Dementia is a clinical syndrome characterized by progressive loss of intellectual abilities, with Alzheimer's disease (AD) being the most common form, accounting for nearly two-thirds of dementia cases in individuals aged 65 years and older. [1,2]. Globally, more than 50 million people live with dementia, with prevalence rates of 4–9% among those aged ≥60 years. [3]. Each year, almost 10 million new cases are diagnosed, and the total burden is projected to triple by 2050, mainly driven by aging populations in low- and middle-income countries. [4,5]. In Indonesia, recent estimates suggest that over 4.2 million individuals are affected. [6].

Clinically, AD is not limited to cognitive decline but also encompasses a spectrum of neuropsychiatric manifestations, collectively referred to as behavioral and psychological symptoms of dementia (BPSD). These include apathy, depression, anxiety, agitation, hallucinations, delusions, and disinhibition, which are prevalent in more than 80% of dementia patients. [7,8]. Such symptoms not only worsen prognosis but also impose a greater burden on caregivers, often being perceived as more distressing than cognitive impairment itself. [9,10]. Despite their clinical significance, the biological mechanisms underlying BPSD remain incompletely understood.

The AT(N) framework provides a biological classification of AD, with amyloid-β deposition (A), tau pathology (T), and neurodegeneration (N) serving as its hallmarks. [9]. Phosphorylated tau at threonine-181 (pTau181) is a central biomarker reflecting tau-related pathology and neurofibrillary tangle formation, a defining feature of AD. [11]. Plasma pTau181 has emerged as a promising minimally invasive biomarker that correlates with amyloid and tau pathology as assessed by PET and can distinguish AD from other neurodegenerative conditions. [12,13]. Levels of plasma pTau181 increase early in the disease course and track disease progression [11].

Previous studies exploring the relationship between tau pathology and neuropsychiatric symptoms have yielded inconsistent results. Elevated CSF pTau181 levels have been associated with higher Neuropsychiatric Inventory Questionnaire (NPI-Q) scores longitudinally [14], and specific symptoms such as agitation and aggression have been linked to increased CSF tau [15]. However, other studies failed to find associations between tau biomarkers and mood disturbances, apathy, or sleep problems. [16,17]. More recently, Krell-Roesch et al. (2023) demonstrated that higher plasma pTau181 and pTau217 were associated with increased risk of agitation, appetite changes, and disinhibition in older adults. [18].

Despite these insights, data specifically addressing the link between plasma pTau181 and BPSD in AD remain limited. Clarifying this relationship could provide a better understanding of the pathophysiological basis of neuropsychiatric symptoms and inform clinical strategies for patient management. Therefore, this study aimed to investigate the association between plasma pTau181 levels and BPSD in Alzheimer's dementia.

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Experimental Section

Research Design

This study employed an analytic observational design with a cross-sectional approach, aimed at examining the association between plasma phosphorylated tau at threonine-181 (pTau181) levels and behavioral and psychological symptoms of dementia (BPSD) among patients with Alzheimer's dementia.

Location, Time, Population, Sample, and Research Variables

The study population comprised clinically diagnosed Alzheimer's dementia patients receiving treatment at the outpatient neurology clinics of Dr. M. Djamil Hospital (Padang), Cipto Mangunkusumo Hospital (Jakarta), and Dr. Sardjito Hospital (Yogyakarta). The diagnosis of Alzheimer's disease (AD) was established based on the NIA-AA clinical criteria, supported by neuroimaging findings (CT or MRI) to exclude other structural brain pathologies and to confirm consistency with patterns of neurodegeneration typical of AD. [19]. This study was part of a project entitled "The Role of Plasma Biomarkers Aβ42 and pTau-181 to Detect Alzheimer's Dementia," a collaborative research program funded by the Indonesia Scheme A, which was conducted in 2024.

Sample recruitment was performed consecutively until the minimum requirement was achieved. The sample size was calculated using the formula for unpaired numerical analytic studies, with $\alpha = 0.05$ ($Z\alpha = 1.64$), $\beta = 0.10$ ($Z\beta = 1.28$), and standard deviation (SD) = 9.3 [20], and mean difference (Δ) = 8, resulting in a minimum of 23 participants. After accounting for a 10% potential dropout rate, the target sample was 25 participants. Ultimately, 40 patients fulfilling all eligibility criteria were enrolled. Patients were eligible for inclusion if they had a confirmed diagnosis of Alzheimer's dementia documented in their medical records and provided written informed consent. Participants were excluded if they had a history of Parkinson's disease, stroke, head trauma, intracranial tumor, chronic kidney disease, early-onset psychiatric disorders, or depression.

Sociodemographic (age, sex, and education level) data were extracted from medical records. Cognitive function was assessed using the Montreal Cognitive Assessment – Indonesian version (MoCA-INA) [21]. Dementia severity was evaluated with the Clinical Dementia Rating (CDR) scale. [22]. Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q), which has been previously translated and validated in the Indonesian language. [23].

Venous blood samples (3 mL) were collected, processed, and analyzed for plasma pTau181 levels using enzyme-linked immunosorbent assay (ELISA). We used an ultrasensitive immunoassay by using FineTest EH4701 Human p-tau-181-96T (FineTest, China; Cat. No. EH2685, Sensitivity: 2.813 pg/ml, Intra-Assay precision: CV< 8%, and Inter-Assay precision: CV<10%) according to the manufacturer's protocol. It can detect biomarker levels in plasma with sensitivity down to the picogram per milliliter (pg/mL) range. All samples were processed in collaboration with the Biomedical Laboratory, Faculty of Medicine, Andalas University, the Integrated Research Laboratory, Faculty of Medicine, University of Indonesia, and the Integrated Research Laboratory, Faculty of Medicine, Universitas Gadjah Mada.

Data Processing and Analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Univariate analysis was used to describe participant characteristics. Normality of continuous variables was assessed, with normally distributed data presented as the mean ± standard deviation and non-normally distributed data as the median (interquartile range, IQR). Data normality was assessed using the Shapiro-Wilk test. Between-group comparisons for plasma pTau181 levels were conducted using the Mann–Whitney U test. A p-value of <0.05 was considered statistically significant.

Ethical approval was obtained from the Health Research Ethics Committee RS M. Djamil Padang with the number DP.04.03/D.XVI.10.1/215/2025 in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal guardians before enrollment. Confidentiality and anonymity of participant data were strictly maintained. The research team ensured that participants were fully informed of the study's objectives, procedures, potential risks, and benefits.

Results and Discussion

The baseline characteristics of patients were grouped according to the presence or absence of BPSD, as shown in Tables 1 and 2. A total of 30 patients (75%) presented with BPSD, with NPI-Q severity scores ranging

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from 3 to 22. The frequency and severity of BPSD in dementia patients are strongly influenced by the environment in which they reside. Among community-dwelling individuals, neuropsychiatric symptoms are reported in 56–98% of cases, while the prevalence rises to 91–96% in hospitalized patients or those in long-term care facilities. [24]. Normality testing was performed to evaluate the distribution of the data. The MoCA-INA scores were approximately normally distributed, with a mean of 14.18 ± 6.13. The CDR score represents an ordinal variable with limited categories (1, 2, and 3) corresponding to mild, moderate, and severe dementia, respectively. Thus, it was summarized descriptively using frequencies rather than measures of central tendency. The majority of participants had mild dementia (65%).

Table 1. Baseline characteristics of the study population

Variable	Total (n = 40)
Age	
< 65 years	15 (35%)
≥ 65 years	25 (65%)
Sex	
Male	22 (55.0%)
Female	18 (45.0%)
Education	
≤ 12 years	15 (37.5%)
> 12 years	25 (62.5%)
MoCA-INA Score	14.18 ± 6.13
Severity of Dementia	
Mild	26 (65.0%)
Moderate	6 (15.0%)
Severe	8 (20.0%)
Plasma p-Tau 181 (pg/mL)	20.37 (12.5 – 36.58)

Notes: Data are presented as n (%), mean ± SD, and median (IQR)

The mean age of participants was 65.25 ± 8.7 years, with the youngest participant being 47 years old and the oldest being 82 years old. The majority of participants were 65 years old or older (65%). Patients with Alzheimer's dementia were significantly older compared with those with mild cognitive impairment (MCI) and controls ($p < 0.001$) [25]. Nonetheless, individuals under 65 years of age may also develop Alzheimer's dementia. Although prevalence studies remain limited, researchers estimate that approximately 110 per 100,000 individuals aged 30–64 years experience early-onset dementia. [4]. Early-onset Alzheimer's dementia accounts for about 5–6% of all AD cases, with an incidence of 6.3 per 100,000 persons per year and a prevalence of 24.2 per 100,000 in those aged 45–64 years. Early-onset AD is clinically defined by onset before age 65 and represents the most common cause of early-onset neurodegenerative dementia. [26].

Table 2. Association between baseline characteristics and the presence of BPSD

Variable	Total (n = 40)	BPSD symptoms		p-value
		Present (n = 30)	Absent (n = 10)	
Age				
< 65 years	15 (35%)	10 (66.7%)	5 (33.3%)	0.457*
≥ 65 years	25 (65%)	20 (80.0%)	5 (20.0%)	
Sex				
Male	22 (55.0%)	15 (68.2%)	7 (31.8%)	0.464*
Female	18 (45.0%)	15 (83.3%)	3 (16.7%)	
Education				
≤ 12 years	15 (37.5%)	13 (86,7%)	2 (13.3%)	0.269*
> 12 years	25 (62.5%)	17 (68,0%)	8 (32.0%)	
MoCA-INA Score	14.18 ± 6.13	13.53 ± 6.29	16.10 ± 5.45	0.257**
Severity of Dementia				
Mild	26 (65.0%)	17 (65.4%)	9 (34.6%)	
Moderate	6 (15.0%)	5 (83.3%)	1 (16.7%)	0.375***
Severe	8 (20.0%)	8 (100.0%)	0 (0%)	

Notes: Results are presented as n (%), mean ± SD, and median (min–max).
*Fisher's exact test, ** Independent t-test, *** Kolmogorov–Smirnov Z test.

Although advanced age is the most substantial risk factor, severity does not always increase linearly with age. Alzheimer's disease is not a regular part of aging, and older age alone is insufficient to cause the disease. [4]. Previous studies have suggested that older age increases the risk of BPSD in AD patients,

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including depression, apathy, agitation, and psychosis. [27–29]. However, this study did not find a significant relationship between age (<65 vs. ≥65 years) and BPSD severity. This discrepancy may be attributed to the limited sample size, a relatively narrow age distribution, or the influence of other factors, such as dementia severity or vascular comorbidities. These findings emphasize that chronological age alone is not a determinant of neuropsychiatric symptoms in AD.

Male patients (55%) outnumbered females (45%). This finding is consistent with several studies in India, which also reported a predominance of male patients in clinical cohorts. [30]. However, globally and among the elderly, dementia prevalence is higher in women, with nearly two-thirds of Alzheimer's patients in the U.S. being female. [4]. Demographic characteristics may explain these differences, gender-related healthcare access disparities—where men are more likely to be brought to medical facilities in developing countries—and differences in survival, as women have longer life expectancies. Indeed, studies in nursing home populations have often found higher rates of dementia among women. [31]. These findings suggest that clinical samples may not accurately reflect the true prevalence of the condition. Although previous studies noted that women may have higher risks of developing BPSD, such as depression and psychosis [27,28]No significant association was observed between gender and BPSD severity in that study. This may be due to the limited sample size or because the influences of gender do not act independently of each other.

Around 25 participants (62.5%) had attained an educational level of more than 12 years. While BPSD has been theorized as a maladaptive response influenced by premorbid psychosocial factors such as personality, life experiences, and education, the present study found no significant association between education level and BPSD ($p > 0.05$). This finding aligns with Steinberg et al. (2006), who reported that education level did not significantly influence the expression of BPSD in AD. [32]. These results suggest that education may not be an independent predictor of BPSD and that other factors, such as neuropathological progression, social support, and general health status, should be considered.

The majority of patients had mild dementia (65%). When dementia severity (CDR) was compared across BPSD groups, no significant difference was observed ($p = 0.375$), suggesting that dementia stage alone did not predict the presence of BPSD. This aligns with Jung and Lee (2022), who found inconsistent associations between dementia severity and BPSD, as some symptoms (e.g., delusions, hallucinations) were not strongly correlated with cognitive decline, whereas others (e.g., irritability, appetite changes) were [33]. Conversely, Kazui et al. (2016) reported a clear association, with BPSD—particularly apathy, agitation, and hallucinations—increasing in frequency and severity with higher CDR scores. [34].

Taken together, this study found no significant associations between age, sex, education, or dementia severity and the presence of BPSD in Alzheimer's dementia. An additional ANCOVA analysis was performed to compare plasma pTau181 levels between patients with and without BPSD, controlling for age, years of education, MoCA-INA score, and CDR score. After adjustment, there was no significant difference in plasma pTau181 between the two groups ($F(1,34)=1.29$, $p=0.265$, partial $\eta^2=0.036$). Although Levene's test indicated a marginal violation of variance homogeneity ($p=0.049$), the analysis was retained and interpreted with caution. These results suggest that demographic or cognitive factors did not confound the nonsignificant association between BPSD and plasma pTau181, implying that such variables may not strongly influence BPSD onset or bias its biochemical evaluation.

The absence of BPSD in a subset of patients with Alzheimer's dementia may represent an atypical clinical phenotype with distinct neurobiological or psychosocial characteristics. Previous studies have proposed that BPSD development is multifactorial, involving not only tau-related neurodegeneration but also neuroinflammation, neurotransmitter imbalance, and alterations in limbic and frontal circuits. Therefore, while patients without BPSD may appear clinically different, their underlying tau pathology—as reflected by plasma pTau181—may not differ substantially from that of patients with BPSD.

In this study, most Alzheimer's dementia patients with BPSD presented with more than one symptom of varying severity. The most frequently observed symptom was apathy (76.7%), followed by depression/dysphoria (60%), irritability/lability (56.7%), and sleep and nighttime behavioral disturbances (56.7%). In terms of severity, most BPSD symptoms were classified as moderate, as seen in hallucinations (50% moderate), depression/dysphoria (55.6% moderate), euphoria (100% moderate), disinhibition (83.3% moderate), and irritability (70.6% moderate). Several symptoms, such as agitation/aggression and apathy, were also frequently rated as severe (37.5% and 26.1%, respectively). Meanwhile, symptoms like anxiety tended to appear only in the mild form (100% mild) (Table 3).

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Table 3. Characteristics of BPSD severity

BPSD Component	Frequency n (%)	Severity of BPSD Symptoms (n)		
		Mild	Moderate	Severe
Delusions	1 (3,3%)	0	0	1
Hallucinations	10 (33%)	1	5	4
Agitation/Aggression	16 (53%)	3	7	6
Depression/Dysphoria	18 (60%)	7	10	1
Anxiety	6 (20%)	6	0	0
Euphoria	9 (30%)	0	9	0
Apathy	23 (76.7%)	5	12	6
Disinhibition	12 (40%)	2	10	0
Irritability/Lability	17 (56.7%)	3	12	2
Aberrant Motor Behavior	9 (30%)	3	5	1
Sleep and Nighttime Behavioral Disturbances	17 (56.7%)	5	11	1
Appetite and Eating Disturbances	8 (26.7%)	5	3	0

Note: Results are presented as n (%)

The most prevalent BPSD observed in patients with Alzheimer's dementia in this study was apathy, followed by depression/dysphoria and irritability. This finding is consistent with previous research by Cerejeira (2012), which reported that the most common BPSD include apathy, depression, irritability, agitation, and anxiety. In contrast, euphoria, hallucinations, and disinhibition are relatively rare. [24]. Approximately 50% of patients presented with four or more symptoms simultaneously. Similarly, Laganà (2022) reported that the most frequent BPSD in Alzheimer's dementia were apathy (57.4%), irritability or affective lability (50.5%), and agitation or aggression (42.3%) [35]. These symptoms may manifest as the patients' subjective experiences or be observed and reported by caregivers. The neurobiological explanation for these manifestations involves dysfunction of neurotransmitter systems such as dopamine and serotonin, along with abnormalities in brain regions including the prefrontal cortex and the limbic system. In addition to biological mechanisms, psychosocial and environmental factors also play an essential role in the emergence of BPSD [24,35].

Plasma p-tau181 levels ranged from 4.32 to 97.23 pg/mL, with the median plasma pTau181 level was 19.29 pg/mL (IQR: 11.81-25.05) in patients without BPSD and 20.67 pg/mL (IQR: 11.81- 43.41) in those with BPSD (Table 4). This finding is consistent with previous studies reporting elevated plasma p-tau181 levels in patients with Alzheimer's dementia compared with mild cognitive impairment (MCI) and cognitively healthy populations. A meta-analysis of nine studies from China, involving 11 cohorts and 1,131 patients with Alzheimer's dementia, reported a pooled mean plasma p-tau181 level of 4.48 pg/mL (95% CI: 4.01–5.00; I^2 = 93%). In contrast, four studies including 368 MCI patients reported a mean of 2.86 pg/mL (95% CI: 2.45–3.34; I^2 = 82%), while healthy controls showed a mean of 2.09 pg/mL (95% CI: 1.90–2.30; I^2 = 77%, $p < 0.01$). In a Japanese population study, the interquartile range (IQR) of plasma p-tau181 was 2.58–4.31 pg/mL in PET-positive individuals and 1.32–2.33 pg/mL in PET-negative individuals. [36]. Similarly, in a Canadian healthy population aged 60–80 years, the reference range was reported as 0.9–4 pg/mL. [37].

Table 4. Association between plasma p-Tau181 levels and BPSD symptoms

Variable	Value*	BPSD symptoms*		p**
		Present (n = 30)	Absent (n = 10)	
p-Tau181 plasma levels (pg/mL)	20.37 (12.05-36.58)	20.67 (11.81-43.41)	19.29 (11.87-25.05)	0.310

Notes: * Results are presented as median (IQR); ** Mann–Whitney U test

Plasma p-tau181 has been shown to increase in Alzheimer's dementia compared with cognitively normal individuals and to correlate consistently with Alzheimer's disease (AD) neuroimaging biomarkers such as amyloid-β and tau PET. [38]. The mean plasma p-tau181 levels in our study were lower than those reported in studies using other platforms, such as ALZpath or Fujirebio. [36–38]. These discrepancies likely reflect differences in assay technology, as ELISA-based kits, such as FineTest, may yield lower absolute

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concentrations compared to high-sensitivity Simoa or electrochemiluminescence assays. Nevertheless, the low intra- and inter-assay CV values confirm good within-study reliability, supporting the validity of our biomarker measurements.

The Mann–Whitney U test revealed no significant difference in plasma pTau181 concentrations between patients with and without BPSD ($p = 0.310$). Consistently, the Spearman correlation analysis also showed no significant association between plasma pTau181 levels and total NPI-Q severity scores ($p = 0.949$). Additional exploratory analyses were conducted to examine differences in plasma p-tau181 concentrations between patients with and without each of the five most prevalent BPSD symptoms (apathy, agitation, depression, irritability, and sleep disturbance) using independent samples t-tests. None of these comparisons showed significant differences in plasma p-tau181 levels. After applying Bonferroni correction for multiple comparisons (adjusted significance threshold $p < 0.001$), all results remained nonsignificant (all $p > 0.001$). These findings suggest that tau-related neurodegeneration, as reflected by plasma pTau181, may not directly correspond to the clinical severity or presence of behavioral and psychological symptoms in Alzheimer's dementia. Plasma p-tau181 is a widely validated biomarker for detecting pathological changes in AD and offers a more practical alternative to invasive biomarkers such as cerebrospinal fluid (CSF) analysis or PET imaging. Neuropsychiatric symptoms (NPS) often emerge as early manifestations of AD, sometimes preceding overt cognitive decline. However, accurately measuring behavioral symptoms remains challenging, limiting the ability to establish robust associations between NPS and AD biomarkers. Although plasma p-tau181 serves as a reliable biomarker of tau-related neurodegeneration in Alzheimer's disease, its relationship with neuropsychiatric symptoms appears limited.

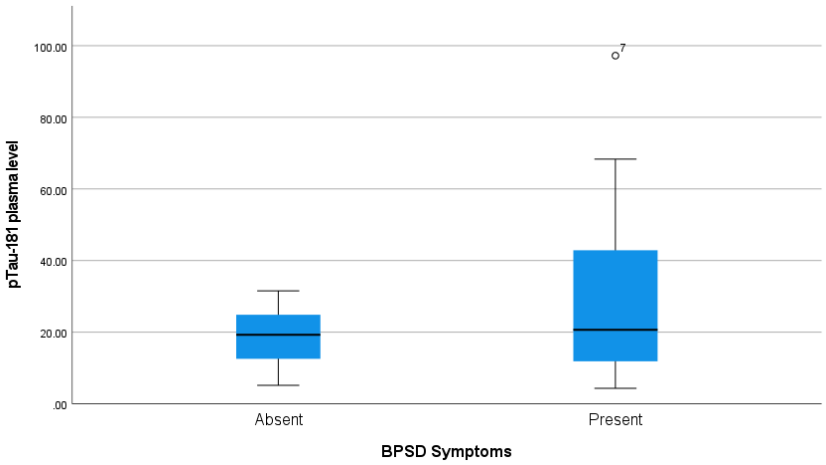

Figure 1. Boxplot of plasma pTau181 concentrations in Alzheimer's dementia patients with and without behavioral and psychological symptoms (BPSD).

In contrast to our findings, Krell-Roesch et al. (2023) used plasma biomarkers and NPI-Q scores to find significant associations between plasma p-tau181 and specific symptoms, such as appetite changes, agitation, and disinhibition, as well as with total NPI-Q severity scores in a large community-based cohort. Other plasma biomarkers, including the Aβ42/Aβ40 ratio and neurofilament light chain (NfL), did not show meaningful associations with behavioral symptoms. These differences may be attributed to variations in the study population and methodology. Their participants represented a broader cognitive spectrum from the community, whereas our sample consisted of clinically diagnosed Alzheimer's dementia patients, likely reflecting a more advanced and homogeneous disease stage. Differences in statistical power and assay sensitivity for plasma biomarkers may also contribute to the discrepancy. These findings highlight that, compared with CSF or neuroimaging biomarkers, plasma biomarkers—particularly p-tau181—tend to show less consistent associations. This may be due in part to the evolving accuracy of plasma biomarker measurement and interpretation in reflecting pathological changes within the brain. [9,18].

Overall, plasma p-tau181 shows only limited associations with NPS. The lack of consistent correlations may reflect the fact that p-tau changes typically emerge later in the disease course and are more strongly related to cognitive decline than to early behavioral symptoms. Some studies suggest that associations between p-tau and NPS may become more evident in advanced dementia stages, whereas in MCI or early AD, the relationship remains unclear. It is also possible that the relatively small sample size and limited variability

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in BPSD severity among participants reduced the power to detect subtle biochemical differences. Future studies with larger samples and multimodal assessments (e.g., combining plasma biomarkers, neuroimaging, and genetic data) are warranted to delineate better the biological substrates underlying the presence or absence of BPSD in Alzheimer's disease. Demographic and psychosocial factors may influence biomarker expression, with potential contributions from genetic background, psychiatric history, and cultural or environmental factors that have yet to be fully explored [39].

Conclusions

This study demonstrated that apathy was the most prevalent behavioral and psychological symptom of dementia (BPSD) among patients with Alzheimer's disease, followed by depression/dysphoria, irritability, and sleep disturbances. In this cross-sectional analysis, no significant difference in plasma p-tau181 levels was observed between patients with and without BPSD. Within the limits of this study, we did not find evidence of a significant association between plasma p-tau181 concentration and the presence of BPSD as a whole. These findings suggest that, in this sample, plasma p-tau181 may primarily reflect neurodegenerative or cognitive processes rather than behavioral and psychological manifestations.

However, several limitations should be considered when interpreting these findings. First, the cross-sectional design precludes any causal inference, making it impossible to determine whether changes in plasma p-tau181 precede or result from the emergence of BPSD. Second, the small sample size and group imbalance reduce statistical power and increase the likelihood of type II error, possibly contributing to the nonsignificant results. Third, the diagnosis of Alzheimer's dementia in this study was clinical and not confirmed by cerebrospinal fluid (CSF) or imaging biomarkers, which could introduce diagnostic heterogeneity. Fourth, potential variability in p-tau181 measurement due to differences in assay performance and pre-analytical handling may affect comparability with other studies. Finally, reliance on the NPI-Q instrument without information on symptom duration or fluctuation limits the ability to capture the full dynamics of BPSD.

Future research using larger, biomarker-confirmed cohorts and longitudinal designs is warranted to clarify the temporal and mechanistic links between tau pathology and behavioral symptoms. Such studies, combined with standardized plasma assays and multimodal biomarker validation, may enhance the interpretability and clinical relevance of plasma p-tau181 in neuropsychiatric research on Alzheimer's disease.

Conflict of Interest

There is no conflict of interest.

Acknowledgment

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