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Original Article

Analysis of Dementia Risks and Biomarker Differences Between Early-Onset and Late-Onset Depression Patients With Age Matching

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Abstract

Background: This study aimed to compare dementia-related peripheral blood biomarkers and cognitive profiles between patients with early-onset depression (EOD) and late-onset depression (LOD) while controlling for age, to clarify their distinct dementia risks and underlying neuropathology. **Methods:** A total of 161 participants aged >60 years were enrolled: EOD, LOD, and age-/sex-matched healthy controls. All patients met DSM-5 criteria for major depressive disorder. Cognitive function was assessed using Mini-Mental State Examination (MMSE), Hopkins Verbal Learning Test-Revised (HVLT-R), Verbal Fluency Test (VFT), Digit Span Test (DST), and Trail Making Test (TMT). Plasma levels of amyloid beta (Aβ)42, Aβ40, phosphorylated tau (p-tau)181, p-tau217, and glial fibrillary acidic protein (GFAP) were measured via chemiluminescence immunoassay. Group comparisons employed analysis of covariance (ANCOVA), adjusting for covariates. **Results:** Both EOD and LOD groups exhibited significant impairments across multiple cognitive domains (TMT-A/B, VFT, DST) compared to healthy controls (HCs) ($p < 0.05$). However, after adjusting for age, sex, and education, no significant differences were observed between EOD and LOD groups. The comparisons between patient groups and HCs remained significant after adjustment. Biomarker analysis revealed significantly lower GFAP and higher p-tau217 levels in both EOD and LOD patients compared to HCs ($p < 0.05$), with no significant difference between the two patient groups. In the depression cohort, GFAP levels negatively correlated with MMSE scores ($r = –0.40$, $p < 0.001$) and negatively correlated with TMT-B completion time ($r = –0.24$, $p = 0.015$), correlations absent in HCs. **Conclusions:** EOD and LOD present with similar severities of cognitive impairment, depressive symptoms, and alterations in specific peripheral Alzheimer's disease (AD) biomarkers. The association between GFAP and cognitive performance suggests its potential role in linking depression with cognitive decline. Comprehensive assessment integrating clinical symptoms, cognition, and peripheral biomarkers in elderly depressed patients, irrespective of onset age, may aid in identifying those at higher risk for neurodegenerative progression.

Keywords: depressive disorder; cognition; biomarker; dementia

Main Points

1. Early-onset depression (EOD) and late-onset depression (LOD) share identical neurocognitive profiles, showing no differences in cognitive function or plasma Alzheimer's disease (AD) biomarkers (glial fibrillary acidic protein (GFAP), p-tau217) when age-matched.

2. Onset age does not differentiate dementia risk in elderly depression; both groups exhibit similar patterns of cognitive impairment and biological alterations.

3. GFAP correlates with cognitive decline, linking astrocytic activation directly to executive dysfunction in depressed patients.

4. Integrated assessment is crucial for identifying high-risk elderly patients, regardless of depression onset age.

1. Introduction

Depression, a multifaceted and globally prevalent mental health disorder, is characterized by significant morbidity, high recurrence rates, substantial disability and mortality, and a considerable disease burden. With the escalating global aging trend, late-life depression (LLD) presents a critical clinical and public health challenge. The prevalence of depression escalates from 5% to a range of 10–20% within the aging demographic [1]. In the geriatric population, depression is linked to functional impairment, a high incidence of cognitive decline, elevated suicide risk, increased mortality rates, diminished quality of life, and a higher likelihood of premature institutionalization in nursing homes [2].

Based on the age of onset, major depressive disorder (MDD) can be categorized into early-onset depression (EOD, first onset before 60 years old) and late-onset depression (LOD, first onset after 60 years old) [3,4]. Prior

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researches have indicated that despite similar clinical presentations, EOD and LOD exhibit differences in etiology, clinical features, sociopsychological characteristics, neurocognitive function, and neural activity [3,4,5,6]. Studies have shown that EOD patients are prone to depressive relapse, significant cognitive impairment, and elevated suicide rates [6,7]. Conversely, individuals with LOD often present with more severe depressive symptoms, autonomic nervous system dysfunction, motor deficits, and memory impairments [6,8]. Cognitive dysfunction is a core feature of depressive disorders, with both groups demonstrating cognitive impairments attributable to distinct etiologies. Meta-analyses reveal that EOD patients primarily experience episodic memory deficits, potentially linked to hypercortisolemia, while LOD patients predominantly exhibit executive function and processing speed deficits [9], which may be associated with microvascular dysfunction, stroke, neurodegeneration, and a high risk of developing Alzheimer's disease [10,11,12].

LLD and dementia exhibit a complex relationship, posing significant diagnostic challenges for clinicians. LLD may elevate the risk of subsequent dementia, or, akin to mild cognitive impairment, serve as a prodromal manifestation of dementia [11,13]. Numerous studies have corroborated the comorbidity of LLD and dementia, suggesting shared pathophysiological mechanisms [11,14]. Consequently, identifying dementia risk factors during the LLD phase is crucial. The differential dementia risk between EOD and LOD remains unclear. Previous studies indicate that late-onset depression elevates the risk of dementia by twofold to fivefold [15,16,17,18]. Early-onset depression might contribute etiologically to dementia onset [19,20] via the degeneration of noradrenaline-producing neurons in the locus coeruleus [21], the attrition of serotonin-producing neurons in the dorsal raphe nuclei [21], the liberation of inflammatory cytokines [22,23], and other possible pathways. Late-onset depression has been proposed as a prodromal manifestation of Alzheimer's disease, with evidence suggesting greater amyloid-beta pathology in LOD compared with early-onset depression [24]. Evidence suggests that LOD is associated with more pronounced hippocampal alterations than EOD [14,25]. Based on the findings from the aforementioned research, it is evident that patients diagnosed with late-onset depression tend to be older, while those with early-onset depression are generally younger. The advanced age of LOD patients, compared to the younger age of EOD patients, may confound the dementia risk due to age-related cognitive decline, a known risk factor for dementia.

The pathophysiology of late-life depression (LLD) remains elusive due to its heterogeneous nature, and the absence of specific diagnostic biomarkers poses a challenge in differentiating it from incipient dementia. Specifically, it remains unclear whether EOD and LOD confer similar risks for dementia, or if variations exist in their associated biomarker profiles. Recent advancements in biomarker research have shifted the diagnostic paradigm of Alzheimer's disease (AD) from a purely symptom-based approach to one incorporating biological criteria [26,27]. Plasma measures of β-amyloid (Aβ42/Aβ40 ratio), phosphorylated tau (p-tau217, p-tau181), and glial fibrillary acidic protein (GFAP) have emerged as the most clinically actionable plasma biomarkers for AD, exhibiting high specificity for AD pathology and strong concordance with PET imaging. Given the established link between depression and AD, coupled with the need for accessible biomarkers, we selected this plasma biomarker panel to capture the multifaceted nature of dementia risk. These markers are consistently implicated in AD pathology and cognitive decline, are readily quantifiable in peripheral blood, and are suitable for large-scale clinical application.

Accordingly, this study recruited age- and depression severity-matched EOD and LOD patients to compare peripheral blood levels of these AD-related biomarkers (Aβ42, Aβ40, p-tau217, p-tau181, and GFAP), alongside comprehensive assessments of cognitive function and depressive symptoms. We posit that EOD and LOD may differ in their cognitive impairment profiles and dementia-related biomarkers, with LOD potentially conferring a higher risk of dementia and implicating distinct AD neuropathological mechanisms. This investigation aims to further elucidate the associated risks of dementia in LLD subtypes and inform clinical practice.

2. Materials and Methods

2.1 Participants

This study was approved by the Ethics Committee of Guangji Hospital, Suzhou, Jiangsu Province, China (Approval No: 2022-001-17). The specific inclusion and exclusion criteria are as follows. Patient group: individuals diagnosed with depression at Guangji Hospital, Suzhou, between October 2022 and August 2025, confirmed through clinical assessment by two psychiatrists with senior professional titles. Inclusion criteria: (1) meeting DSM-5 criteria for major depressive disorder; (2) Han ethnicity, regardless of gender; (3) educational attainment of at least primary school; (4) Hamilton Depression Rating Scale (HDRS, 24-item version) score >20; Young Mania Rating Scale (YMRS) score <6; (5) Mini-Mental State Examination (MMSE) score ≥24 (excluding dementia); (6) Age >60 years at enrollment; EOD was defined as a first depressive episode occurring before age 60, and LOD as a first episode occurring at age 60 or later, regardless of recurrence status. Exclusion criteria encompassed comorbid psychiatric disorders, substance use disorders, significant hepatic, renal, or cardiac dysfunction, neurological conditions such as stroke or dementia, thyroid disorders, new initiation, dose adjustment, discontinuation, or switching of psychotropic or cognitive-altering medications within 4 weeks prior to baseline assessment, communication or au-

ditory impairments, and physical conditions that could precipitate depressive episodes, including anemia or hypothyroidism. Participants maintained on stable long-term antidepressants or benzodiazepines for depressive or anxiety disorders were eligible for enrolment. The detailed information regarding the scales and diagnostic instruments used in this study is provided in the **Supplementary Material**.

2.2 Clinical Assessments

Demographic variables included gender, age, marital status, and educational attainment. Clinical variables encompassed age at initial onset, episode frequency, presence of precipitating factors for the first episode, current pharmacotherapy, and medical history. The severity of depressive symptoms was quantified using the HDRS. Anxiety severity was measured with the Hamilton Anxiety Rating Scale (HAMA). Global cognitive functioning was appraised via the MMSE. Additionally, multiple cognitive domains—including verbal learning, attention, interference resistance, memory, and executive functioning were evaluated using the Hopkins Verbal Learning Test-Revised (HVLT-R), Verbal Fluency Test (VFT), Digit Span Test (DST), and Trail Making Tests A and B (TMT-A, TMT-B). All assessments were conducted by two trained clinical psychiatrists who demonstrated inter-rater reliability through concordance testing. The detailed information regarding assessment tools used in this study is provided in the Supplementary Material.

2.3 Measurement of Plasma Biomarkers

All subjects underwent fasting venipuncture between 7:00 and 9:00 AM, with sample transportation completed within one hour, followed by centrifugation at 1610 ×g for 15 minutes. Plasma specimens were stored at –80 °C and prepared through thawing, vortexing, and recentrifugation prior to biomarker quantification. Plasma levels of Aβ42, Aβ40, p-tau181, p-tau217 and GFAP were quantified using the fully automated chemiluminescence immunoassay platform Elf 2910 (Vazyme, Nanjing, Jiangsu, China), utilizing specific reagent kits including Vazyme β-Amyloid 1–40 Plasma (catalog number M1705CB), Vazyme β-Amyloid 1–42 Plasma (catalog number M2705CB), Vazyme p-tau 181 Plasma (catalog number P3701CB), Vazyme p-tau 217 Plasma (catalog number P4701CB) and GFAP (catalog number M5705CB). All procedures conformed to the manufacturer's protocols, with duplicate analyses and internal standards employed to ensure analytical precision and reproducibility.

2.4 Statistical Analysis

This investigation utilized IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA) for statistical analysis. Group comparisons of baseline demographic, clinical, and cognitive characteristics (Table 1) were performed using one-way ANOVA for continuous variables and χ^2 tests for categorical variables, without covariate adjustment. To examine independent group effects on plasma biomarkers and cognitive measures, analysis of covariance (ANCOVA) was conducted, adjusting for age, sex, and education (years). These covariates were selected as they may influence cognitive performance and biomarker levels. To control for multiple comparisons, post hoc pairwise analyses were performed using the Bonferroni correction (adjusted $\alpha = 0.05$ / number of pairwise tests) to evaluate statistical differences in cognitive metrics and biomarker levels between cohorts. Effect sizes for ANCOVA are reported as partial η^2 (small $\geq$0.01, medium $\geq$0.06, large $\geq$0.14). For significant group effects, post-hoc pairwise comparisons were performed, and Cohen's d was calculated as $(M_1 - M_2) / \sqrt{(\text{MSerror})}$ (small $\geq$0.2, medium $\geq$0.5, large $\geq$0.8). In addition, to compare the correlations between biomarker levels and clinical features as well as cognitive function, the data were processed by z-score normalization and used in a general linear model (GLM), with bilateral testing and a significance criterion set at $p < 0.05$. The correlation analyses were exploratory in nature and therefore not corrected for multiple comparisons; accordingly, the significant correlations should be interpreted with caution. The reporting of this study followed the STROBE guidelines for observational studies. The completed STROBE checklist is provided as **Supplementary Material**.

3. Results

3.1 Demographic and Clinical Characteristics

This study included a total of 50 participants with EOD, 59 with LOD, and 52 healthy controls (HCs). Based on prior studies ($d \approx 0.65$), $\geq$48 participants per group was required for 80% power at $\alpha = 0.05$. Our sample met this criterion. Baseline age of depression, gender distribution, educational attainment, and cultural background showed no significant differences between early-onset and late-onset depression groups ($p > 0.05$), with both groups age- and sex-matched to healthy controls. Both patient groups exhibited varying degrees of antidepressant and benzodiazepine usage, with no significant difference in medication utilization rates. Clinically, early-onset depression patients had a significantly earlier mean age of onset (50.8 years), compared to late-onset patients (66.6 years). Correspondingly, early-onset cases had longer illness duration and higher recurrence frequency. In assessments using the Hamilton Depression and Anxiety Rating Scales, total scores did not differ significantly between groups.

3.2 Cognitive Evaluation

Both depression groups demonstrated notable impairments across multiple cognitive domains. As illustrated in Table 1, patients with EOD and LOD performed significantly worse than HCs on TMT-A, TMT-B, VFT, and forward digit span test (DST-f). On the backward digit span test (DST-b), only the LOD group scored significantly

Table 1. Demographic, clinical and medication information of older adults with major depressive disorders and healthy controls.

Demographics	Late-life depression patients		Healthy controls	Statistic		
	EOD (N = 50)	LOD (N = 59)	N = 52	F/χ^2/t	*p*	Post hoc
Age, mean (SD)	71.22 (4.45)	73.14 (4.83)	71.37 (5.59)	2.57	0.08	
Sex				0.16	0.93	
Male	21	26	21			
Female	29	33	31			
Years of education, mean (SD)	10.46 (3.02)	10.37 (3.14)	10.81 (2.78)	0.32	0.73	
Plasma biomarker						
Aβ42 (pg/mL)	6.69 (1.42)	6.78 (1.48)	6.99 (2.04)	0.45	0.64	
Aβ40 (pg/mL)	137.42 (13.97)	137.22 (18.58)	132.42 (18.04)	1.44	0.24	
Aβ42/Aβ40	0.049 (0.012)	0.051 (0.015)	0.054 (0.018)	1.22	0.3	
p-tau181 (pg/mL)	3.47 (1.47)	3.73 (1.28)	3.70 (1.31)	0.58	0.56	
p-tau217 (pg/mL)	3.69 (1.31)	3.72 (0.98)	2.96 (0.97)	8.34	<0.001	A, B>C
GFAP (pg/mL)	132.59 (11.29)	129.71 (10.08)	140.57 (8.78)	16.86	<0.001	A, B<C
Cognition						
MMSE	24.96 (1.73)	24.32 (2.05)	27.81 (1.68)	54.84	<0.001	A, B<C
TMT-A	138.48 (9.55)	129.78 (11.23)	91.60 (10.05)	301.59	<0.001	A, B>C
TMT-B	177.98 (11.78)	175.76 (10.73)	119.08 (10.31)	490.38	<0.001	A, B>C
VFT	10.58 (2.03)	9.92 (2.01)	18.03 (2.88)	199.08	<0.001	A, B<C
DST-f	6.14 (1.36)	6.02 (1.38)	7.89 (1.19)	33.38	<0.001	A, B<C
DST-b	4.40 (1.39)	3.58 (0.86)	5.42 (0.96)	40.08	<0.001	B<C
HVLT-R	20.40 (1.99)	20.70 (1.70)	21.60 (3.23)	3.55	0.031	A<C
Medication information				EOD vs. LOD		
Antidepressants	31/50	39/59		0.11	0.76	
Benzodiazepines	29/50	37/59		0.33	0.69	
Clinical characteristics						
Age of onset	50.8	66.6		280.82	<0.001	
Duration of illness, years	20.41 (6.09)	6.53 (3.90)		208.89	<0.001	
Number of Previous Episodes	4.44 (1.37)	2.92 (1.32)		35.06	<0.001	
HDRS, mean (SD)	31.92 (5.12)	31.58 (4.24)		0.14	0.71	
HAMA, mean (SD)	26.10 (5.78)	28.03 (4.83)		3.65	0.059	

Abbreviations: SD, Standard Deviation; YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale; EOD, early-onset depression; LOD, late-onset depression; Aβ, beta-amyloid; p-tau, phosphorylated Tau; GFAP, glial fibrillary acidic protein; MMSE, Mini-Mental State Examination; TMT, Trail Making Test; VFT, Verbal Fluency Test; DST-f, forward digit span test; DST-b, backward digit span test; HVLT-R, Hopkins Verbal Learning Test-Revised; HAMA, Hamilton anxiety rating scale; A, EOD; B, LOD; C, healthy controls. F and *p* values are from unadjusted one-way ANOVA or χ^2 tests, presented for descriptive purposes. Adjusted analyses are reported in the Results section.

lower than HC. For HVLT-R scores, the EOD group differed significantly from HC, whereas the LOD group did not. To control for potential demographic confounding, we re-analyzed these cognitive outcomes using ANCOVA adjusting for age, sex, and education. The overall pattern of group differences remained consistent after covariate adjustment, confirming that the observed cognitive impairments are robust to demographic factors. After adjusting for education, age, and gender, no significant differences persisted across cognitive domains between late-onset and early-onset depression groups.

3.3 Peripheral Biomarker Analysis

Among the six biomarkers evaluated, one-way ANOVA revealed that the mean levels of GFAP in peripheral blood significantly differed across the three study groups ($F = 16.86$, $p < 0.001$, partial $\eta^2 = 0.176$). Specifically, both early-onset and late-onset depression groups exhibited markedly lower GFAP levels compared to healthy controls (EOD vs. HC: $p < 0.001$, Cohen's $d = 0.79$; LOD vs. HC: $p < 0.001$, Cohen's $d = 1.07$). Following Bonferroni correction for multiple comparisons, no significant difference was observed between the early-onset and late-onset depression groups themselves ($p > 0.05$, Cohen's $d = 0.29$). Similarly, plasma p-tau217 concentrations in peripheral blood were significantly elevated in both the early-

onset and late-onset depression groups relative to healthy controls ($F = 8.34$, $p < 0.001$, partial $\eta^2 = 0.096$; EOD vs. HC: $p = 0.003$, Cohen's d = 0.67; LOD vs. HC: $p = 0.001$, Cohen's d = 0.70). However, there was no statistically significant difference between the two depression groups regarding p-tau217 levels, indicating similar biomarker profiles among these patient subgroups. To control for potential demographic confounding, we further re-analyzed group differences in these biomarkers using ANCOVA with age, sex, and education (years) as covariates. After adjustment, the overall pattern of group differences remained consistent with the unadjusted ANOVA results: both EOD and LOD groups continued to show significantly lower GFAP and higher p-tau217 compared to HC, with no significant difference between the two depression subgroups. Among the three covariates, age appeared to have the greatest influence on GFAP levels. Nevertheless, the overall pattern of group differences in both GFAP and p-tau217 remained unchanged after adjustment, indicating that the observed biomarker alterations are not driven by demographic confounding.

3.4 Biomarker–Behavior Correlations

We elucidated the link between biomarkers and depressive behavioral phenotypes via correlation analysis on the combined depressed sample (EOD and LOD), as no significant group differences were observed between subtypes and to maintain adequate statistical power for these exploratory analyses. A correlation matrix of cognitive measures and biological markers revealed significant associations between GFAP levels and MMSE, TMT-B scores in elderly depressed patients (Fig. 1). Specifically, GFAP showed a strong negative correlation with MMSE ($r = -0.40$, $p < 0.001$) (Fig. 2a) and a weak negative correlation with TMT-B ($r = -0.24$, $p = 0.015$) (Fig. 2b). A trend between GFAP and the DST-f was not statistically significant ($p = 0.072$). No such relationships were found in healthy controls ($p > 0.05$). Clinical characteristics like age of onset, illness duration, or episode number did not correlate significantly with these biomarkers ($p > 0.05$). Due to the limited sample size, we did not perform separate correlation analyses for EOD and LOD subgroups, as the absence of significant baseline differences and concerns regarding statistical power suggested that such analyses would be unlikely to yield stable or generalizable results.

4. Discussion

This study comparatively analyzed peripheral blood biomarkers for dementia diagnosis and staging between early-onset and late-onset depression under age-matched conditions. Our primary findings are: (1) Both early-onset and late-onset geriatric depression patients exhibit significant impairments across global and multiple sub-cognitive domains; (2) Under conditions matched for age, sex, and educational attainment, no significant differences

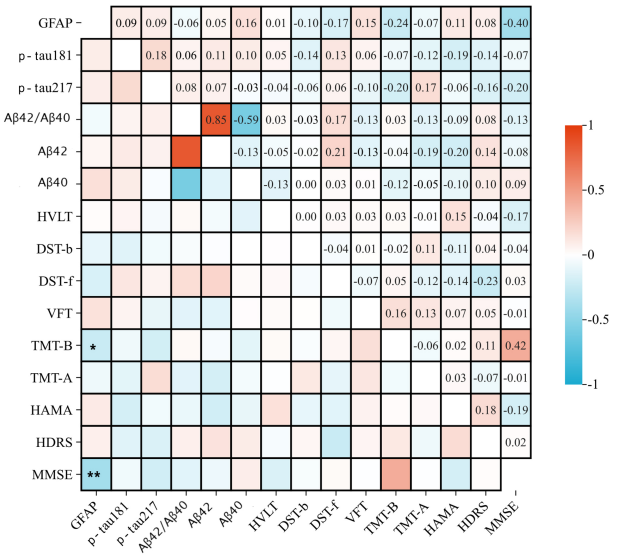

Fig. 1. Behavior–biomarker correlation matrix. Notes: the heat map shows the correlations between peripheral blood biomarkers and cognitive assessments/clinical features in depressed patients. *$p < 0.05$, **$p < 0.01$. GFAP, glial fibrillary acidic protein; MMSE, Mini-Mental State Examination; TMT, Trail Making Test; VFT, Verbal Fluency Test; DST-f, forward digit span test; DST-b, backward digit span test; HVLT-R, Hopkins Verbal Learning Test-Revised; HDRS, Hamilton depression rating scale; HAMA, Hamilton anxiety rating scale.

between patient groups were found in cognitive impairment, depressive or anxiety severity; (3) Regarding peripheral blood biomarkers, both patient groups had significantly higher P-Tau217 and lower GFAP levels than healthy controls, while other biomarkers showed no differences; (4) GFAP levels negatively correlated with MMSE and TMT-B scores, a correlation absent in controls.

Prior research confirms cognitive impairments in depression, particularly in older adults [1,2,18], potentially increasing dementia risk. Differentiating depression from early dementia is clinically challenging. While AD diagnostics integrate biological and clinical markers across stages [27], AD biomarkers could help distinguish elderly depression's psychological symptoms from AD. In our study, late-onset depression patients showed deficits in verbal learning, attention, interference resistance, memory, and executive function versus healthy controls. However, no significant differences emerged between the two groups across these domains. This finding may contrast with previous reports. Liu et al. [28] reported higher MMSE scores in early-onset depression compared to late-onset depression. He et al. [29] found that late-onset depression was associated with poorer reasoning and problem-solving skills than early-onset depression, while early-onset depression showed poorer social cognition. Our study matched early-onset depression patients with a late-onset group at enroll-

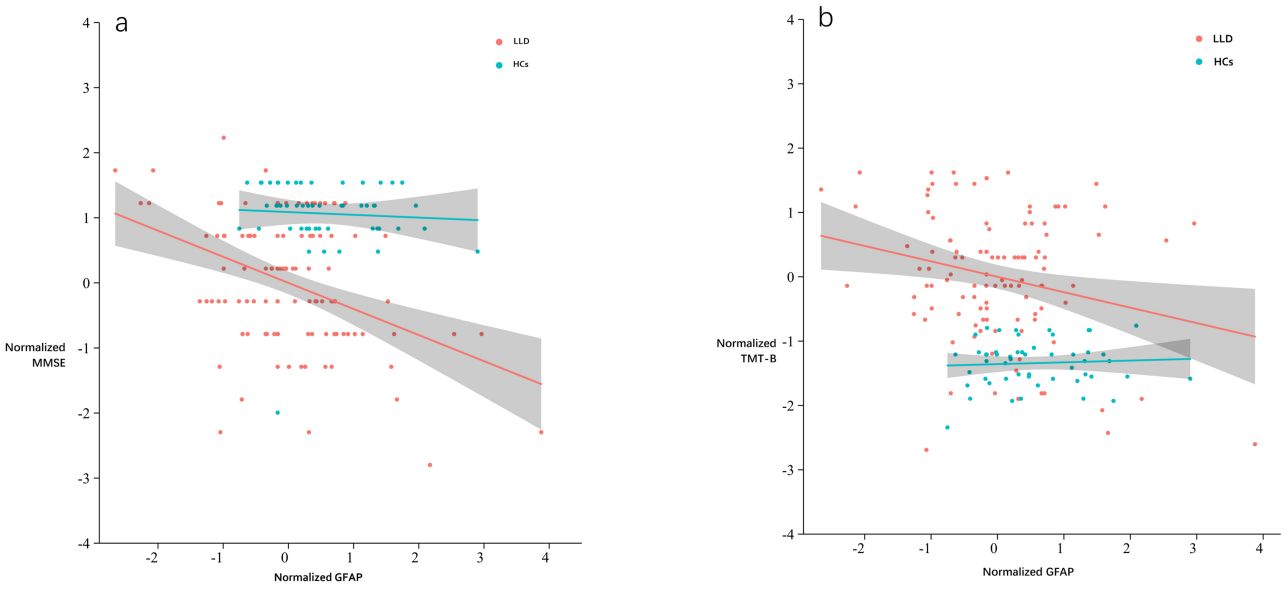

Fig. 2. Correlational analyses between cognitive function and GFAP in depressed patients and Healthy controls. Notes: (a) illustrates the correlation between GFAP and MMSE scores in the LLD group (r = –0.40, $p < 0.001$) and the HCs group (r = –0.06, $p > 0.05$). (b) shows the correlation between GFAP and TMT-B scores in the LLD group (r = –0.24, $p = 0.015$) and the HCs group (r = –0.11, $p > 0.05$). GFAP, glial fibrillary acidic protein; MMSE, Mini-Mental State Examination; TMT, Trail Making Test; LLD, late-life depression; HCs, healthy controls.

ment, resulting in older age brackets for early-onset participants. This contrasts with previous literature, which predominantly included younger and middle-aged cohorts, potentially explaining divergent findings. By aligning age groups, our study controls for age, and aging severity influences on depressive symptomatology.

Our analysis of elderly depressed patients revealed no significant differences in Hamilton Depression Rating Scale or anxiety scale scores between early- and late-onset depression groups, despite the early-onset group exhibiting earlier onset, longer duration, and more frequent episodes. This contrasts with some literature suggesting later-onset depression presents with more severe symptoms, autonomic dysfunction, memory deficits, and better treatment response [6,8]. Our data indicate similar symptom severity and cognitive impairment in late-life early-onset patients compared to their late-onset counterparts. This highlights the heterogeneity of depression, where different age groups may manifest with distinct disease presentations and cognitive symptoms, potentially driven by varying biological mechanisms, with age likely playing a crucial role in this process.

Extensive prior research has investigated the link between Alzheimer's disease hallmarks—amyloid-beta (Aβ) and tau—and depression, yielding inconsistent results [30,31,32,33,34]. Regarding Aβ, systematic reviews confirm that non-demented elderly individuals with depressive symptoms exhibit significantly elevated Aβ levels and a higher prevalence of amyloid positivity compared to non-depressed controls [33,34]. within mild cognitive impairment (MCI) cohorts, this correlation appears attenuated or inverse, with depressive symptoms failing to correlate with increased amyloid burden [34]. Regarding tau pathology, a 2016 meta-analysis found no significant overall association with depression [31]; however, multiple PET studies reveal region-specific Tau deposition in the inferior temporal lobe and entorhinal cortex among cognitively normal individuals with depressive symptoms [30,32]. Collectively, these findings suggest a complex, stage-dependent interplay between Aβ and tau pathologies and depressive symptoms, potentially mediated by regional tau distribution rather than global burden.

In older adults with depression, peripheral blood p-tau-217 was significantly elevated, though no biomarker correlated with depressive severity. Prior tau research, predominantly PETCT-based, yielded positive findings [32,35,36], but peripheral blood studies are limited. Some studies in older depressed cohorts found no abnormalities in Tau, p-tau181, Tau/Aβ42 ratio, and p-tau181/Aβ42 ratios, nor correlations with depressive symptomatology [37,38]. However, other research reported significant differences in p-tau, and Aβ1-42/p-tau ratios between individuals with MCI and older depressed patients with MCI [39]. In summary, there are limited reports on peripheral blood tau217 in geriatric depression, and our study's restricted sample size necessitates cautious interpretation of findings. Further large-scale, longitudinal investigations are required for validation.

GFAP, a brain-specific astrocyte biomarker with minimal extraneural sources [40], is detected at very low serum levels in healthy individuals. Neurological insults trigger astrocyte disintegration, leading to GFAP release into circulation and aiding early diagnosis of various neurological conditions, including stroke and neurodegenerative diseases [41,42,43]. Recent studies indicate altered GFAP levels in psychiatric disorders [44,45,46]. Our findings reveal significant GFAP reduction in both early- and late-onset depression, consistent with prior postmortem and cerebrospinal fluid (CSF) studies showing regional GFAP immunoreactivity variations in the prefrontal cortex [47,48]. These findings support astrocytic pathology in depression and the vascular depression hypothesis. While multiple studies report lower peripheral GFAP [37,46,47] in depressed patients correlating with severity [46,49], a recent meta-analysis found no significant difference in unipolar depression, though it noted positive findings in bipolar disorder [50]. Overall, these subgroup comparisons were exploratory and lacked sufficient statistical power for equivalence testing. Future studies with larger, more balanced samples—incorporating CSF or molecular imaging measures—are warranted to directly validate the link between peripheral AD-related biomarkers and central pathological changes in depression subtypes, and to determine whether true biological or cognitive differences exist between early- and late-onset depression.

This study indicates a significant correlation between peripheral GFAP levels and cognitive function, aligning with prior findings in AD and major depressive disorder. Circulating GFAP levels serve as a valuable biomarker for detecting MCI and AD [51]. Levels of serum GFAP not only correlate with MMSE scores but also predict the likelihood of MCI progression to AD [52]. Elevated GFAP levels have been associated with diminished memory and compromised white matter microstructure [53]. GFAP measured in serum may aid in assessing the severity of depression and refining diagnostic protocols for major depressive disorder. Desai et al. [49] identified an additive effect of depressive symptomatology on the association between the logarithm of GFAP and global cognitive function. Notwithstanding equivocal evidence, the presented data indicate that in the therapeutic management of late-life depression, a comprehensive assessment encompassing depressive symptomatology, cognitive deficits, and peripheral blood biomarkers is paramount. Such a multifaceted diagnostic paradigm may facilitate the identification of individuals at heightened risk for Alzheimer's Disease, thereby enabling timely therapeutic interventions to attenuate neurocognitive deterioration.

Intriguingly, we observed a divergent biomarker profile in both depression subgroups, characterized by decreased GFAP alongside elevated p-tau217. This dissociation, rarely reported in geriatric depression, contrasts with the concurrent rise of these markers in typical AD. We interpret this 'glial–tau decoupling' as a potential depression-specific signature: the reduction in GFAP may reflect astrocytic dysfunction or exhaustion secondary to chronic stress and inflammation [47,54], while elevated p-tau217 likely indicates emerging AD-related pathology or kinase dysregulation [55]. We therefore caution that this pattern requires validation with more data, and that future studies should explore whether this dissociation predicts a unique cognitive trajectory in depressed patients.

Limitations

Despite these discoveries, their interpretation requires careful consideration due to inherent study constraints, underscoring the necessity for further research. First, this cross-sectional study's modest sample size and lack of longitudinal tracking limit robustness and generalizability. Future longitudinal studies are needed to determine if peripheral biomarkers predict dementia differently in EOD versus LOD. Second, antidepressant and hypnotic use in elderly patients may have influenced cognitive function and biomarkers, a factor not entirely excluded. Third, the small subgroup sizes precluded stratification by cognitive impairment severity. Future research should stratify patients by cognitive impairment degree in EOD and LOD to better understand the interplay of age, cognition, and biological markers. Fourth, the correlation analyses between biomarkers and cognitive measures were performed without correction for multiple comparisons, increasing the risk of Type I error. Thus, these findings should be considered exploratory and interpreted with appropriate caution. Finally, it is important to note that plasma biomarker levels reflect a complex interplay of central nervous system (CNS) production, peripheral clearance, and systemic factors. Thus, our peripheral findings should be interpreted as preliminary evidence of peripheral-to-central cross-talk, rather than a direct proxy of brain pathology.

5. Conclusions

In conclusion, our results suggest that both early- and late-onset depression cohorts exhibit significant cognitive deficits compared to controls, with no inter-group differences after covariate adjustment. Analyses of peripheral blood revealed consistently lower GFAP and elevated p-tau217 in both depression groups relative to controls. Notably, GFAP inversely correlated with cognitive function in elderly depressed patients. These findings suggest similar peripheral biomarker profiles in depression regardless of onset and highlight the overlap between elderly depression, cognitive impairment, and the predementia stage. Peripheral blood biomarkers can be considered a tool for assessing the severity of cognitive impairment in patients with late-life depression. Given the cross-sectional design, our findings should be considered preliminary and clinical application is premature; however, comprehensive assessment of clinical symptoms, cognitive function, and peripheral AD

biomarkers is warranted in all elderly depressed patients, irrespective of onset age, to effectively identify or exclude early or prodromal Alzheimer's disease.

Availability of Data and Materials

The data underlying this article will be shared upon reasonable request to the corresponding authors.

Author Contributions

HG: writing—review & editing, writing—original draft, investigation, conceptualization. XZ: writing—review & editing, investigation, formal analysis. XW: writing—review & editing, methodology, investigation, formal analysis, Validation. HS: writing—review & editing, methodology, investigation. XY: writing—review & editing, investigation, formal analysis, project administration, funding acquisition. DW: writing—review & editing, Supervision, project administration, funding acquisition, conceptualization. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Guangji Hospital, Suzhou, Jiangsu Province, China (Approval No: 2022-001-17). A written informed consent form, approved by the Ethics Committee, was provided to and signed by each participant prior to any study-related procedures. The study was carried out in accordance with the guidelines of the Declaration of Helsinki.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/AP50936.

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