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Original Article

Predictive value of beta amyloid, phosphorylated Tau, neurofilament light chain, and glial fibrillary acidic protein for depression in Alzheimer's disease

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Abstract: Objectives: To investigate differences in biochemical markers and their association with depressive symptoms in patients with Alzheimer's disease (AD) with and without concurrent depression. Methods: In this retrospective case-control study, 329 AD patients admitted to Beijing Panjiayuan TCM-Western Integrated Hospital between May 2019 and May 2022 were included. Patients were categorized into a comorbid depression group (n=167) and a non-depression group (n=162) based on Cornell Scale for Depression in Dementia (CSDD) scores. Biochemical markers, including β-amyloid proteins (Aβ1-42, Aβ1-40), phosphorylated Tau proteins (p-Tau181, p-Tau217), neurofilament light chain protein (NfL), glial fibrillary acidic protein (GFAP), and inflammatory cytokines, were measured and statistically analyzed. Results: High-density lipoprotein cholesterol (HDL-C) was significantly lower in the comorbid depression group (P<0.001). Levels of Aβ1-42 (P=0.012), Aβ1-40 (P=0.006), p-Tau181 (P=0.003), p-Tau217 (P=0.003), NfL (P<0.001), and GFAP (P=0.008) were significantly elevated in the depression group compared to the non-depression group. Additionally, interleukin-10 (P=0.004) and interleukin-6 (P=0.047) levels were higher, while interleukin-1β (P<0.001) was lower in the comorbid depression group. Receiver operating characteristic curve identified HDL-C (area under the curve [AUC]=0.602), p-Tau217 (AUC=0.595), NfL (AUC=0.692), GFAP (AUC=0.580), and IL-1β (AUC=0.600) as significant predictors of depression severity. Conclusions: Specific biochemical markers, including HDL-C, Aβ42/40, p-Tau217, NfL, GFAP, and IL-1β, are independently associated with depression in AD patients. A combined biomarker model may improve prediction of comorbid depression in AD and provide guidance for personalized treatment.

Keywords: Alzheimer's disease, depression, predictive value, biochemical markers

Introduction

Alzheimer's Disease (AD), one of the most prevalent neurodegenerative disorders, is characterized by progressive cognitive decline [1]. Depressive symptoms are frequently observed in AD patients, and these symptoms not only accelerate disease progression but also diminishe patients' quality of life [2]. However, the underlying pathological mechanisms and biochemical markers associated with comorbid depression in AD patients remain poorly understood [3-5]. Accumulating evidence suggests that depressive symptoms in AD patients may be associated with changes in certain biomarkers, such as beta-amyloid protein (Aβ), phosphorylated Tau protein (p-Tau), neurofilament light chain protein (NfL), and various inflammatory cytokines [6].

Previous studies have also indicated that changes in high-density lipoprotein cholesterol (HDL-C) may be associated with depression in AD, but the specific mechanisms required further exploration [7]. The Aβ1-42/Aβ1-40 ratio is recognized as an important indicator for assessing AD progression, but its role in AD with depression has been poorly investigated [8]. Meanwhile, p-Tau181 and p-Tau217, key markers of tau pathology, have drawn attention for their potential involvement in depression among AD patients [9]. Recent studies also

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suggest that elevated levels of NfL and glial fibrillary acidic protein (GFAP) might indicate more severe neurodegenerative changes [10, 11].

Additionally, inflammatory factors such as interleukin-1β (IL-1β), IL-6, and IL-10 play important roles in AD-related depression. IL-1β, a pro-inflammatory cytokine, is closely associated with neuroinflammation and AD pathology [12]. IL-6 and IL-10 are key regulators of immune responses, and their abnormal levels reflect chronic inflammatory states [13]. Elevated levels of IL-6 and IL-10 have been correlated with the onset and progression of depression [14, 15]. Although the specific roles of these cytokines in AD-related depression remain debated, their alterations appear to be involved in AD pathology and may serve as indicators of comorbid depression. These findings highlight the potential importance of inflammatory factors in the mechanisms underlying AD-related depression.

This study aimed to investigate the levels of specific biomarkers and inflammatory factors in AD patients using a retrospective case-control design, and to analyze their relationship with comorbid depression. We further sought to identify biomarkers with significant predictive value for comorbid depression in AD and to establish a predictive model integrating multiple biomarkers. Such a model not only facilitates early intervention but also provides scientific evidence to support personalized treatment plans.

Materials and methods

Case selection

This retrospective case-control study included 329 AD patients admitted to Beijing Panjiayuan TCM-Western Integrated Hospital from May 2019 to May 2022. Demographic and clinical information was collected from the hospital medical record system. As a retrospective study, the sample size was determined by the number of eligible patients during the study period. All procedures involving human participants complied with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Beijing Panjiayuan TCM-Western Integrated Hospital with informed consent waived.

Inclusion and exclusion criteria

Inclusion criteria: (1) Memory deficit complaints reported by patients or their guardians; (2) Ability to cooperate with physical examinations and neuropsychological tests; (3) Brain atrophy confirmed by computed tomography (CT) or magnetic resonance imaging (MRI); (4) Clinical diagnosis of AD according to the National Institute on Aging and Alzheimer's Association (NIA-AA) criteria [16]; (5) Age >60 years.

Exclusion criteria: (1) Subjective cognitive complaints with objective impairment in cognitive testing, but Clinical Dementia Rating (CDR) scores=0 [17]; (2) Presence of other organic or functional brain diseases; (3) Coexistence of other serious neurological disorders; (4) Positive family history of dementia; (5) Recent use of drugs that may affect biomarker levels.

Grouping

According to the Cornell Scale for Depression in Dementia (CSDD) scores [18], the patients were divided into two groups: the comorbid depression group (n=167; CSDD score >8) and non-depression group (n=162; CSDD score ≤8). The follow-up for all patients was completed by January 2025 to ensure data consistency and completeness.

Biochemical markers determination

Cerebrospinal fluid (CSF) collection and analysis: Cerebrospinal fluid (CSF) was obtained via lumbar puncture within 24 hours of patient admission. The samples were immediately centrifuged at 1200×g for 10 minutes, aliquoted, and stored at -80°C until analysis. Enzyme-linked immunosorbent assay (ELISA) was used to measure β-amyloid protein 1-42 (Aβ1-42), β-amyloid protein 1-40 (Aβ1-40), phosphorylated Tau181 protein (p-Tau181), phosphorylated Tau217 protein (p-Tau217), NfL, and GFAP, intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM). Additionally, the Aβ1-42/Aβ1-40 (42/40) ratio was calculated. Inflammation associated marker proteins were measured by Meso Quickplex SQ120 (MSD, USA) and obtained values were normalized against total protein concentration (pg/mg).

The reagent kits used included Aβ1-42 ELISA Kit (842701, BioLegend, USA), Aβ1-40 ELISA

Kit (842801, BioLegend, USA), p-Tau181 ELISA Kit (849601, BioLegend, USA), p-Tau217 ELISA Kit (842801, BioLegend, USA), Simoa p-Tau217 Advantage Kit (Quanterix, USA), Simoa NF Light SR-X ELISA Kit (103400, Quanterix Corporation, USA), Human GFAP Quantikine ELISA Kit (DGFA00, R&D Systems (Bio-Techne), USA), ICAM (ab309183, Abcam, USA) and VCAM (ab47355, Abcam, USA) kits.

Serum collection and HDL-C measurement: Fasting venous blood samples were collected from all patients, centrifuged to separate serum, and stored at -80°C until analysis. HDL-C concentration was determined using the Wako HDL-Cholesterol E kit (Fujifilm Wako Pure Chemical Corporation, Japan). Serum samples were diluted according to the kit's instructions, added to the reaction wells with enzyme reagents, thoroughly mixed, and incubated at 37°C for 10 minutes. The reactions were then terminated, and absorbance was measured at 492 nm using a microplate reader. HDL-C concentrations were calculated based on the standard curve.

Statistical method

All statistical analyses were conducted using SPSS 29 software (SPSS Inc., Chicago, IL, USA) and R software package 3.0.2 (Free Software Foundation, Boston, MA, USA). Continuous variables with normal distribution were expressed as mean ± standard deviation (mean ± SD), and between-group comparisons were performed using independent-samples t tests. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test as appropriate. In addition, univariate and multivariate logistic regression analyses were conducted to calculate odds ratio (OR) and 95% confidence interval (CI) for potential risk factors. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive value of biomarkers, and the area under the curve (AUC) was calculated. The statistical significance level was set to $P<0.05$.

Results

Comparison of general information between the two groups of patients

No significant differences were observed between the two groups in terms of age (t=1.100, P=0.272), gender distribution (χ^2=0.242, P=0.623), number of children (χ^2=0.001, P=0.979), place of residence (χ^2=0.003, P=0.954), living alone status (χ^2=0.008, P=0.930), smoking habits (χ^2=4.751, P=0.093), alcohol consumption habits (χ^2=2.774, P=0.250), or education level (χ^2=4.640, P=0.098). By contrast, the total CSDD score was markedly higher in the comorbid depression group compared to the non-depression group (13.56±1.46 vs 5.46±1.06, t=57.735, P<0.001), confirming a markedly greater burden of depressive symptoms in the comorbid group. The details are shown in **Table 1**.

Comparison of clinical characteristics between the two groups of patients

As shown in **Table 2**, no significant differences were observed between the two groups in terms of body mass index (BMI) (25.34±3.67 kg/m^2 vs 24.97±3.24 kg/m^2, t=0.949, P=0.343), apolipoprotein E ε4 (APOE ε4) allele distribution (χ^2=0.439, P=0.803), disease course duration (2.91±1.01 years vs 2.85±1.04 years, t=0.574, P=0.567), disease staging (χ^2=0.026, P=0.999), total cholesterol levels (5.45±1.02 mmol/l vs 5.64±1.01 mmol/l, t=1.717, P=0.087), systolic blood pressure (143.32±23.35 mmHg vs 145.14±21.16 mmHg, t=0.743, P=0.458), or diastolic blood pressure (79.25±10.34 mmHg vs 78.75±10.95 mmHg, t=0.421, P=0.674). However, HDL-C levels were notably lower in the comorbid depression group compared to the non-depression group (1.26±0.46 mmol/l vs 1.43±0.43 mmol/l, t=3.446, P<0.001).

Comparison of biochemical markers between the two groups of patients

The comparison of biochemical markers between the groups is presented in **Figure 1**. Levels of Aβ1-42 (19.76±9.67 pg/ml vs 21.94±5.05 pg/ml, t=2.546, P=0.012), Aβ1-40 (225.67±50.81 pg/ml vs 238.05±25.06 pg/ml, t=2.789, P=0.006), and the Aβ1-42/Aβ1-40 ratio (0.09±0.03 vs 0.08±0.03, t=2.926, P=0.004) were significantly higher in the comorbid depression group compared with the non-depression group. Similarly, levels of p-Tau181 (4.26±1.64 pg/ml vs 4.88±2.05 pg/ml, t=3.025, P=0.003), p-Tau217 (3.07±1.34 pg/ml vs 3.43±0.66 pg/ml, t=3.019, P=0.003), NfL (43.66±15.76 pg/ml vs 58.16±21.67 pg/ml, t=6.959, P<0.001), and GFAP (48.86±17.72

Table 1. Comparison of general information between the two groups

Parameters	Non-depression group (n=162)	Comorbid depression group (n=167)	t/χ^2	p
Age (years)	70.45±3.65	69.95±4.56	1.100	0.272
Gender [n (%)]			0.242	0.623
Male	82 (50.62%)	80 (47.90%)		
Female	80 (49.38%)	87 (52.10%)		
Education Level (years) [n (%)]			4.640	0.098
Primary or below	59 (36.42%)	56 (33.53%)		
Secondary School	76 (46.91%)	67 (40.12%)		
College or above	27 (16.67%)	44 (26.35%)		
Number of children [n (%)]			0.001	0.979
≤2	123 (75.93%)	127 (76.05%)		
>2	39 (24.07%)	40 (23.95%)		
Place of residence [n (%)]			0.003	0.954
Urban	80 (49.38%)	83 (49.70%)		
Rural	82 (50.62%)	84 (50.30%)		
Live alone [n (%)]			0.008	0.930
Yes	91 (56.17%)	93 (55.69%)		
No	71 (43.83%)	74 (44.31%)		
Smoking [n (%)]			4.751	0.093
Never	57 (35.19%)	41 (24.55%)		
Former	84 (51.85%)	97 (58.08%)		
Current	21 (12.96%)	29 (17.37%)		
Alcohol consumption [n (%)]			2.774	0.250
Never	47 (29.01%)	36 (21.56%)		
Former	84 (51.85%)	100 (59.88%)		
Current	31 (19.14%)	31 (18.56%)		
CSDD total score	5.46±1.06	13.56±1.46	57.735	<0.001

Note: CSDD, Cornell Scale for Depression in Dementia.

Table 2. Comparison of clinical characteristics between the two groups

Parameters	Non-depression group (n=162)	Comorbid depression group (n=167)	t/χ^2	p
BMI [kg/m^2]	25.34±3.67	24.97±3.24	0.949	0.343
APOE ε4 [n (%)]			0.439	0.803
0 alleles	77 (47.53%)	85 (50.90%)		
1 allele	46 (28.4%)	46 (27.54%)		
2 alleles	39 (24.07%)	36 (21.56%)		
Disease course (years)	2.91±1.01	2.85±1.04	0.513	0.608
Disease staging [n (%)]			0.026	0.999
Mild Cognitive Impairment	21 (12.96%)5	22 (13.17%)		
Mild AD	53 (32.72%)	54 (32.34%)		
Moderate AD	63 (38.89%)	66 (39.52%)		
Severe AD	25 (15.43%)	25 (14.97%)		
Total cholesterol (mmol/l)	5.45±1.02	5.64±1.01	1.713	0.088
HDL-C (mmol/l)	1.43±0.43	1.26±0.46	3.494	<0.001
Systolic blood pressure (mmHg)	143.32±23.35	145.14±21.16	0.741	0.459
Diastolic blood pressure (mmHg)	79.25±10.34	78.75±10.95	0.427	0.670

Note: BMI, body mass index; APOE, apolipoprotein E; AD, Alzheimer's Disease; HDL-C, high-density lipoprotein cholesterol.

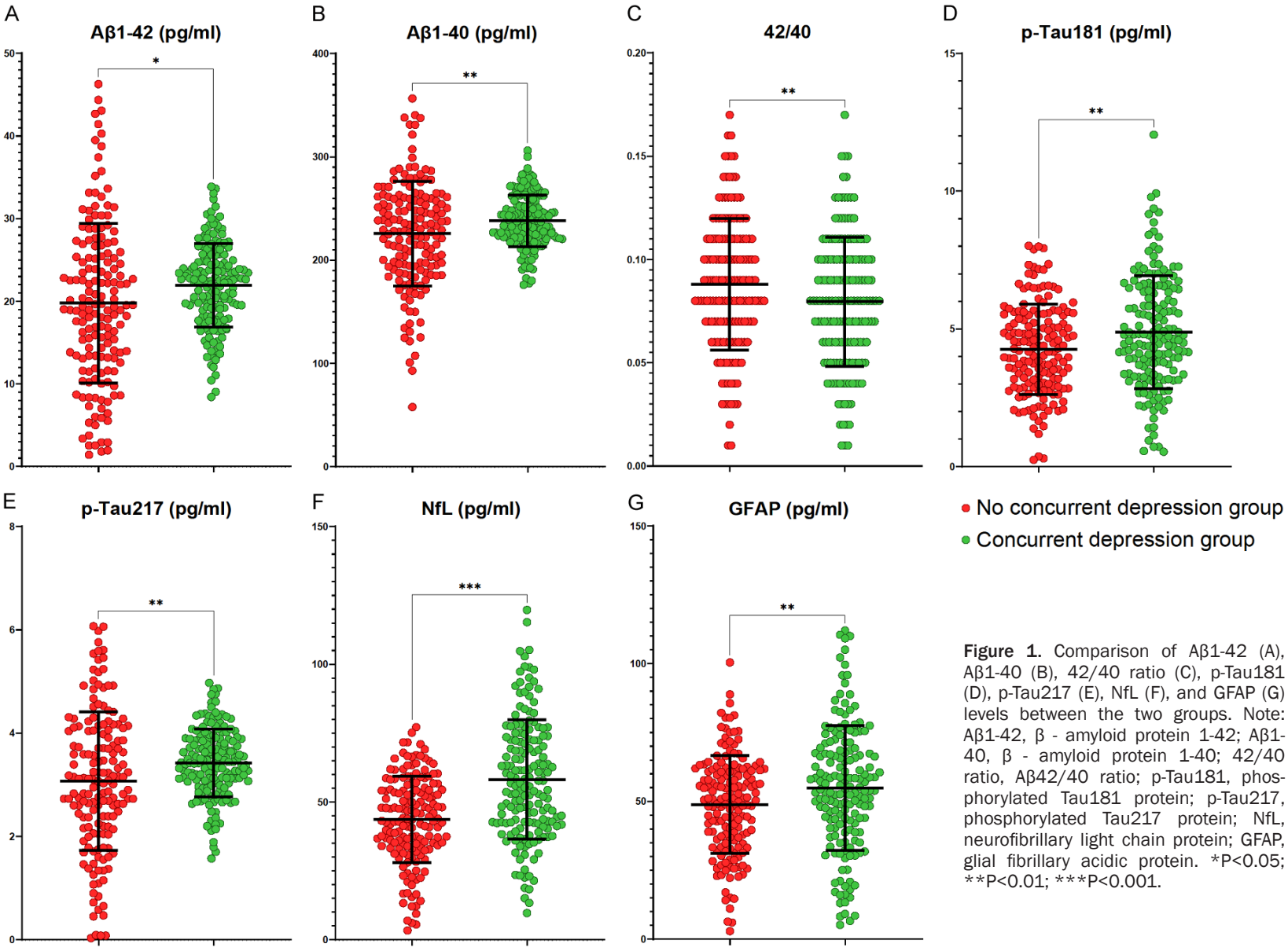


Figure 1. Comparison of Aβ1-42 (A), Aβ1-40 (B), 42/40 ratio (C), p-Tau181 (D), p-Tau217 (E), NfL (F), and GFAP (G) levels between the two groups. Note: Aβ1-42, β - amyloid protein 1-42; Aβ1-40, β - amyloid protein 1-40; 42/40 ratio, Aβ42/40 ratio; p-Tau181, phosphorylated Tau181 protein; p-Tau217, phosphorylated Tau217 protein; NfL, neurofibrillary light chain protein; GFAP, glial fibrillary acidic protein. *P<0.05; **P<0.01; ***P<0.001.

pg/ml vs 54.85±22.61 pg/ml, t=2.677, P=0.008) were all significantly higher in the comorbid depression group. The significantly higher levels of these biochemical markers highlight the potential role of depression as a factor contributing to the progression or severity of AD, emphasizing the importance of considering depressive symptoms in the clinical management and treatment strategies for these patients.

The comparison of inflammatory cytokine levels between the two groups of patients is shown in **Figure 2**. Specifically, patients in the comorbid depression group demonstrated significantly higher levels of IL-10 (31.64±7.42 vs 29.21±7.62×10^{-3} pg/mg, t=2.933, P=0.004) and IL-6 (0.50±0.12 vs 0.48±0.09 pg/mg, t=1.993, P=0.047) but significantly lower IL-1β levels (69.43±5.78 vs 71.52±5.58×10^{-3} pg/mg, t=3.338, P<0.001) compared with those without depression. No significant differences were observed in other cytokines, including IL-4, IL-13, IFN-γ, IL-2, IL-8, IL-12p70, and TNF-α (all P>0.05).

In addition, comparisons of endothelial markers revealed no significant group differences in the levels of ICAM (6.06±1.67 vs 6.35±2.05 ng/mL, t=1.443, P=0.150) or VCAM (6.34±1.41 vs 6.69±2.12 ng/mL, t=1.756, P=0.080) (**Table 3**).

Correlation analysis

Correlation analysis between biochemical markers and depression severity in AD patients is presented in **Table 4**. HDL-C (ρ=-0.176, P=0.001), Aβ42/40 (rho=-0.158, P=0.004), and IL-1β (rho=-0.173, P=0.002) showed significant negative correlations with depression scores. In contrast, Aβ1-42 (ρ=0.160, P=0.004), Aβ1-40 (ρ=0.127, P=0.021), P-Tau181 (ρ=0.147, P=0.008), P-Tau217 (ρ=0.165, P=0.003), NfL (ρ=0.332, P<0.001), GFAP (ρ=0.138, P=0.012), IL-10 (ρ=0.151, P=0.006), and IL-6 (ρ=0.118, P=0.033) exhibited significant positive correlations with depression.

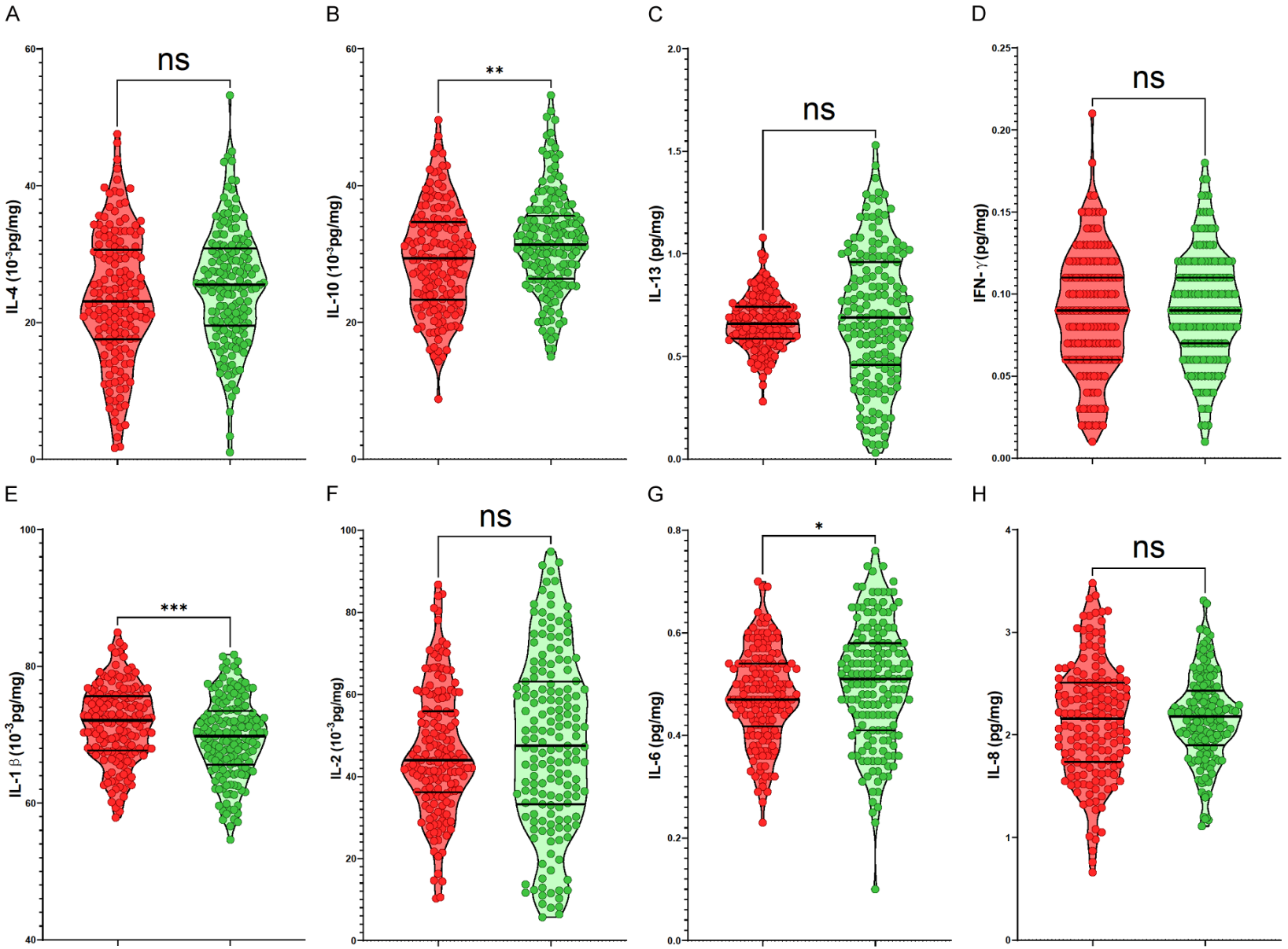
Regression analysis of biochemical markers and depression in AD patients

In univariate analysis, HDL-C (P<0.001; OR=0.416; 95% CI: 0.247-0.686), Aβ1-42 (P=0.012; OR=1.038; 95% CI: 1.009-1.069), Aβ1-40 (P=0.006; OR=1.008; 95% CI: 1.002-1.014), Aβ42/40 ratio (P=0.004; OR=0.000; 95% CI: 0.000-0.038), p-Tau181 (P=0.003; OR=1.198; 95% CI: 1.064-1.355), p-Tau217 (P=0.003; OR=1.382; 95% CI: 1.120-1.721), NfL (P<0.001; OR=1.042; 95% CI: 1.029-1.057), GFAP (P=0.009; OR=1.015; 95% CI: 1.004-1.026), IL-10 (P=0.004; OR=1.044; 95% CI: 1.014-1.076), and IL-1β (P=0.001; OR=0.937; 95% CI: 0.900-0.974) were significantly associated with depression levels.

In multivariate analysis, HDL-C (P=0.009; OR=0.448; 95% CI: 0.246-0.818), Aβ42/40 ratio (P=0.014; OR=0.000; 95% CI: 0.000-0.130), p-Tau217 (P<0.001; OR=1.578; 95% CI: 1.207-2.062), NfL (P<0.001; OR=1.049; 95% CI: 1.032-1.065), GFAP (P=0.024; OR=1.015; 95% CI: 1.002-1.029), and IL-1β (P=0.017; OR=0.944; 95% CI: 0.900-0.990) remained significant (**Table 5**). These findings suggest that multiple biomarkers - particularly those related to lipid metabolism (HDL-C), amyloid processing (Aβ42/40 ratio), tau phosphorylation (p-Tau217), neurodegeneration (NfL), glial activation (GFAP), and inflammatory response (IL-1β), are independently associated with depression severity in AD patients, highlighting their potential as predictive factors for comorbid depression.

Receiver operating characteristic (ROC) curve analysis

ROC curve analysis was conducted to evaluate the predictive performance of biochemical markers for comorbid depression in AD patients (**Figure 3**). NfL showed the highest discriminatory power, with AUC of 0.692 at a best threshold of 60.505, sensitivity of 0.455, specificity of 0.858, and a Youden index of 0.313 (F1 score=0.568). Other markers with moderate predictive ability included Aβ1-42 (AUC=0.592; best threshold=16.390; sensitivity=0.874; specificity=0.370; Youden index=0.244; F1 score=0.704), 42/40 (AUC=0.573; best threshold=0.075; sensitivity=0.665; specificity=0.463; Youden index=0.104; F1 score=0.376), p-Tau217 (AUC=0.595; best threshold=2.845; sensitivity=0.826; specificity=0.457; Youden index=0.283; F1 score=0.702), and IL-1β (AUC=0.600; best threshold=72.485; sensitivity=0.731; specificity=0.457; Youden index=0.188; F1 score=0.315). HDL-C (AUC=0.602;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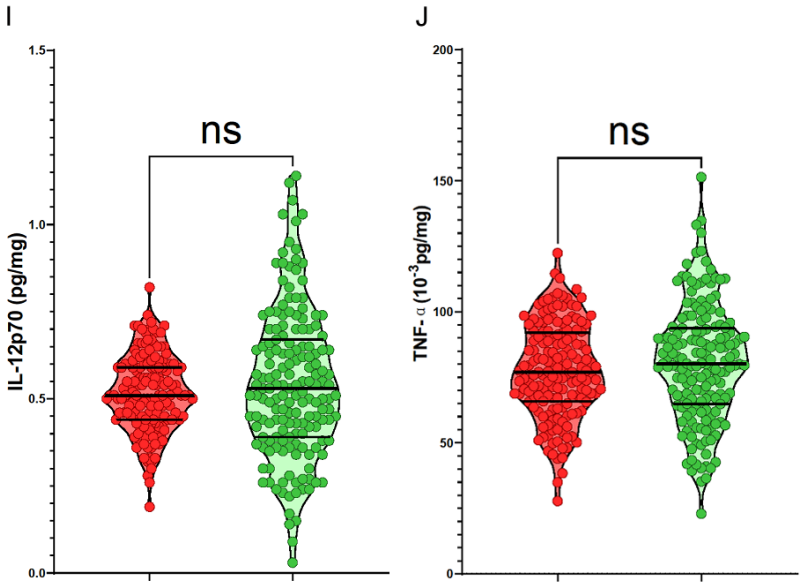

Figure 2. Comparison of inflammatory cytokine levels between the two groups. Note: A: IL-4; B: IL-10; C: IL-13; D: IFN-γ; E: IL-1β; F: IL-2; G: IL-6; H: IL-8; I: IL-12p70; J: TNF-α. IL, interleukin; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha. Ns, no significant; *P<0.05; **P<0.01; ***P<0.001.

Table 3. Comparison of endothelial markers between the two groups

Parameters	Non-depression group (n=162)	Comorbid depression group (n=167)	t	p
ICAM (ng/mL)	6.06±1.67	6.35±2.05	1.443	0.150
VCAM (ng/mL)	6.34±1.41	6.69±2.12	1.756	0.080

Note: ICAM, Intercellular Adhesion Molecule; VCAM, Vascular Cell Adhesion Molecule.

Table 4. Correlation analysis between biochemical markers and depression in Alzheimer's disease patients

Variable	rho	P
HDL-C	-0.176	0.001
Aβ1-42	0.160	0.004
Aβ1-40	0.127	0.021
42/40	-0.158	0.004
p-Tau181	0.147	0.008
p-Tau217	0.165	0.003
NfL	0.332	<0.001
GFAP	0.138	0.012
IL-10	0.151	0.006
IL-1β	-0.173	0.002
IL-6	0.118	0.033

Note: Aβ1-42, β - amyloid protein 1-42; Aβ1-40, β - amyloid protein 1-40; p-Tau181, phosphorylated Tau181 protein; p-Tau217, phosphorylated Tau217 protein; NfL, neurofibrillary light chain protein; GFAP, glial fibrillary acidic protein; 42/40, calculate Aβ1-42/Aβ1-40; IL, interleukin.

best threshold=1.055; sensitivity=0.335; specificity=0.864; Youden index=0.199; F1 score=0.531) and IL-6 (AUC=0.568; best threshold=0.505; sensitivity=0.515; specificity=0.636; Youden index=0.151; F1 score=0.551) also showed moderate discriminatory capacity, albeit with lower sensitivities or specificities.

Overall, these results suggest that NfL provides the strongest predictive value for identifying comorbid depression in AD patients, supported by its superior AUC and relatively balanced sensitivity and specificity. However, other markers like Aβ1-42, p-Tau217, and IL-1β also demonstrated potential utility, underscoring the multifactorial nature of depression in AD and the likely contribution of multiple pathophysiological processes.

Establishment of a combined prediction model

A combined biomarker model was constructed for predicting comorbid depression in AD patients (**Figure 4**). As shown in **Figure 4A**, the out-of-bag (OOB) error rate decreased and stabilized as the number of trees increased in the random forest, indicating reliable model performance without overfitting. **Figure 4B** presents the variable importance ranking, in which NfL, p-Tau217, Aβ1-42, and HDL-C emerged as the most influential predictors, highlighting the critical roles of neurodegeneration, tau phosphorylation, amyloid processing, and lipid metabolism. **Figure 4C** displays the ROC curve of the model, which achieved strong discriminatory power with an AUC of 0.823, significantly higher than individual indicators. These results collectively suggest that integrating multiple biomarkers enhances the diagnostic accuracy for detecting comorbid depression in AD patients, providing a basis for early detection and targeted therapies.

Discussion

In this retrospective case-control study, we conducted a multidimensional analysis of AD patients with and without comorbid depression, identifying significant differences in biochemical markers and clinical characteristics. These findings not only deepen our understanding of the pathological mechanisms of AD with comorbid depression but also provide new perspectives for future research and clinical practice.

Regarding biochemical markers, our results showed that AD patients with comorbid depression exhibited significantly higher levels of Aβ1-42, Aβ1-40, p-Tau181, p-Tau217, NfL, and GFAP. These results are consistent with previous studies, supporting the notion that these biomarkers may play significant roles in the pathological processes of AD with depression. Notably, increases in NfL and GFAP suggest more severe neurodegenerative changes [9, 19]. NfL, as a sensitive marker of axonal injury, has been extensively reported to be associated with a wide range of neurological diseases [20]. Similarly, GFAP, a marker of astrocytic activation, reflects glial reactivity and neuroinflamma-

Table 5. Multivariate regression analysis of comorbid depression in Alzheimer's disease patients

Parameters	Univariate analysis			Multivariate analysis		
	P	OR	95% CI	P	OR	95% CI
HDL-C	<0.001	0.416	0.247-0.686	0.009	0.448	0.246-0.818
Aβ1-42	0.012	1.038	1.009-1.069	0.139	1.026	0.992-1.062
Aβ1-40	0.006	1.008	1.002-1.014	0.049	1.007	1.000-1.013
42/40 ratio	0.004	0.000	0.000-0.038	0.014	0.000	0.000-0.130
p-Tau181	0.003	1.198	1.064-1.355	0.077	1.139	0.986-1.314
p-Tau217	0.003	1.382	1.120-1.721	<0.001	1.578	1.207-2.062
NfL	<0.001	1.042	1.029-1.057	<0.001	1.049	1.032-1.065
GFAP	0.009	1.015	1.004-1.026	0.024	1.015	1.002-1.029
IL-10	0.004	1.044	1.014-1.076	0.150	1.026	0.991-1.063
IL-1β	0.001	0.937	0.900-0.974	0.017	0.944	0.900-0.990
IL-6	0.049	8.114	1.027-67.203	0.099	8.466	0.672-106.722

Note: OR, odds ratio; CI, confidence interval.

tion in the AD brain [21]. Interestingly, although both Aβ1-42 and Aβ1-40 levels were significantly elevated in the comorbid depression group, their ratio did not show obvious differences, indicating the complex pathological processes in AD with concurrent depression.

Secondly, we observed that HDL-C levels were significantly lower in AD patients with depression compared to those without. This finding is consistent with previous report, suggesting that disturbances in lipid metabolism may represent a key feature of depression in AD [22]. Earlier studies indicated that lower HDL-C levels are linked to a higher risk of depression, possibly through disruption of cerebral lipid homeostasis and neurotransmitter regulation [23]. Additionally, changes in HDL-C levels have been connected to inflammatory procession, which might worsen the progression of AD [24, 25].

Moreover, our study showed that IL-10 and IL-6 levels were significantly elevated, whereas IL-1β levels were markedly reduced in AD patients with comorbid depression. These results indicate that specific inflammatory pathways contribute to the onset and progression of AD with concurrent depression. Elevated IL-10 and IL-6 likely reflect a chronic inflammatory state, which has been strongly associated with depression [26]. Conversely, the reduction in IL-1β suggests a more complex milieu in neuroinflammation and AD pathology [27]. These findings further underscore the significance of inflammatory responses in the pathophysiology of AD with concurrent depression and provide a theoretical rationale for exploring anti-inflammatory therapeutic approaches.

Notably, our regression analysis identified several biomarkers significantly linked to depressive symptoms in AD, including HDL-C, Aβ1-42, Aβ1-40, the Aβ42/40 ratio, p-Tau217, NfL, GFAP, IL-10, IL-1β, and IL-6. These findings provide a solid foundation for the development of predictive models. Specifically, p-Tau217 and NfL remained significant in multivariate analysis, indicating their potential as independent predictors of comorbid depression in AD. Earlier research showed that p-Tau217 demonstrates high sensitivity and specificity for early AD diagnosis, whereas NfL proved to be a reliable marker for tracking neurodegenerative changes [28, 29]. The present findings suggest that these markers may also be clinically relevant for identifying AD patients at risk of depression.

The predictive model incorporating NfL, p-Tau217, and other key biomarkers demonstrated high diagnostic accuracy and considerable clinical value. These biomarkers enable clinicians to better stratify patients at risk for comorbid depression, allowing for earlier intervention and more individualized management strategies. Such an approach could improve patient outcomes by facilitating timely diagnosis and targeted therapies, potentially slowing the progression of both AD and depressive symptoms. Additionally, integrating multiple biomarkers into a single predictive model

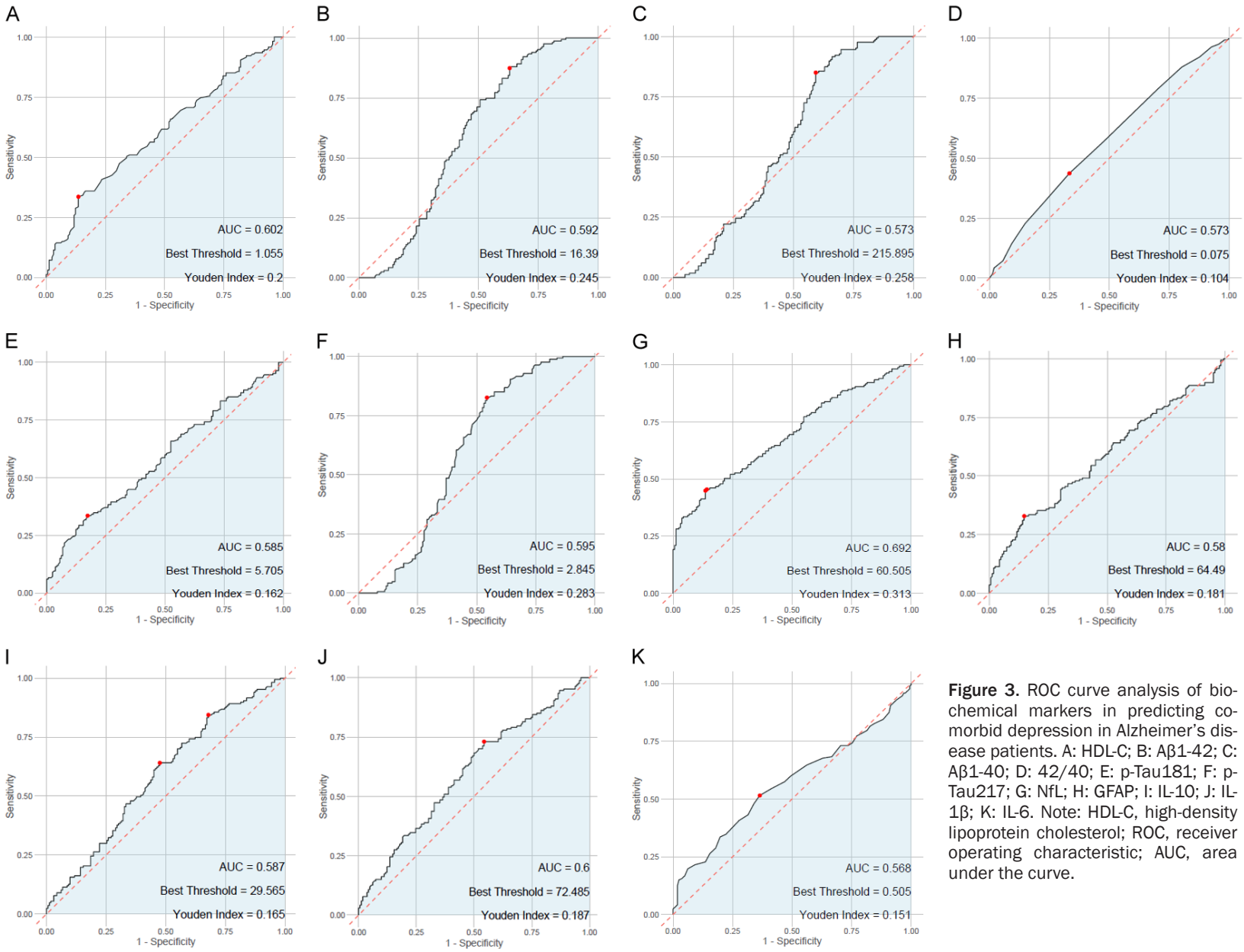

Figure 3. ROC curve analysis of biochemical markers in predicting comorbid depression in Alzheimer's disease patients. A: HDL-C; B: Aβ1-42; C: Aβ1-40; D: 42/40; E: p-Tau181; F: p-Tau217; G: NfL; H: GFAP; I: IL-10; J: IL-1β; K: IL-6. Note: HDL-C, high-density lipoprotein cholesterol; ROC, receiver operating characteristic; AUC, area under the curve.

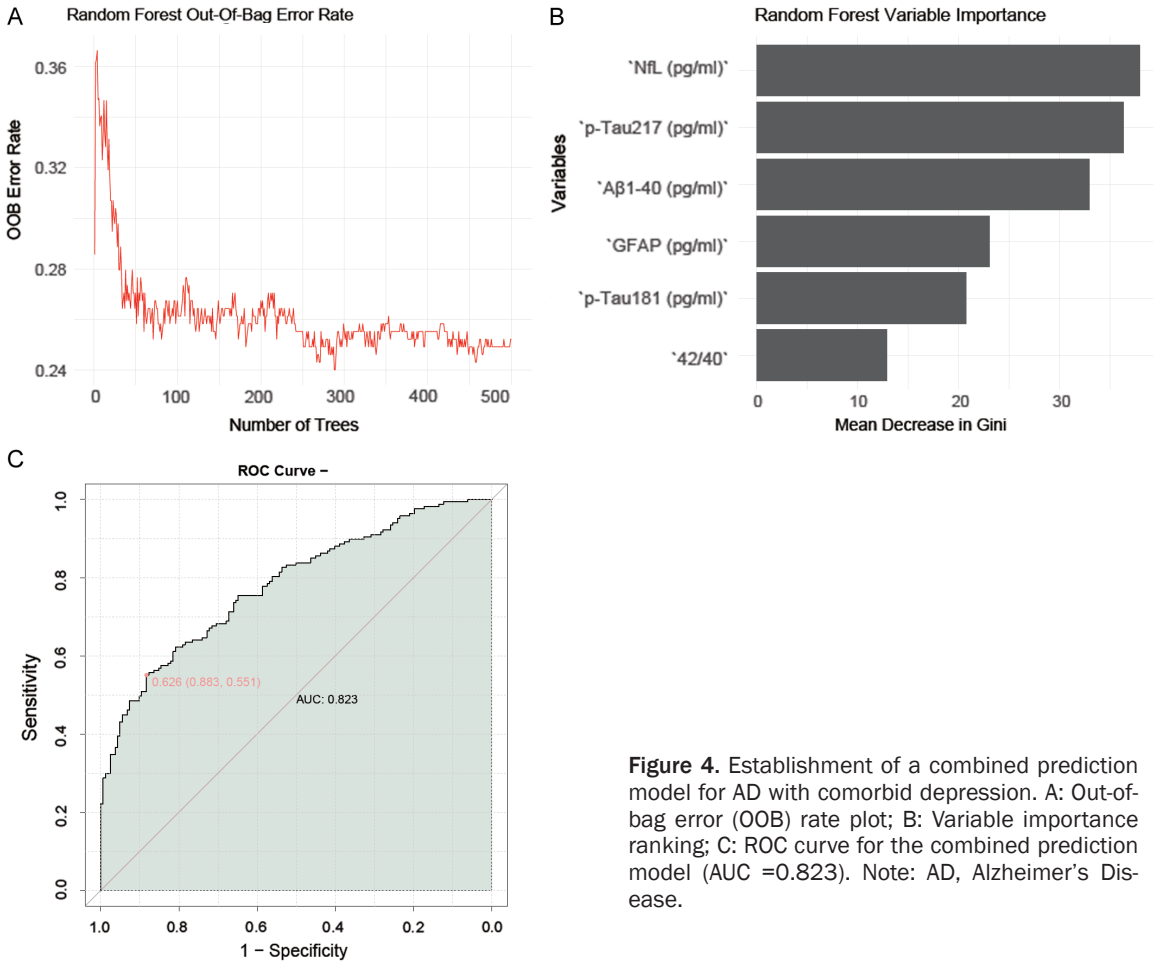

Figure 4. Establishment of a combined prediction model for AD with comorbid depression. A: Out-of-bag error (OOB) rate plot; B: Variable importance ranking; C: ROC curve for the combined prediction model (AUC =0.823). Note: AD, Alzheimer's Disease.

enhances our understanding of the complex interplay between neurodegeneration, inflammation, and mood disturbances in AD. This provides valuable insights into the development of future therapeutic approaches.

Our study offers important insights into the role of specific biomarkers in predicting depression in AD patients; however, several limitations deserve attention. First, the retrospective design could have introduced potential selection biases. Future prospective, large-scale, and multicenter studies are needed to validate our findings and assess the robustness of the predictive model across diverse populations. Second, although we identified several key biomarkers, other molecular pathways and clinical factors likely contribute to the development of depression in AD. Incorporating these additional variables may further enhance the predictive accuracy of biomarker-based models. Finally, while our model demonstrated promising discriminatory power, its clinical applicability requires further validation in real-world settings before routine implementation. Future research should therefore focus on translating these findings into clinical practice to optimize the management of AD patients with comorbid depression.

Conclusion

This study identified significant differences in several biochemical markers between AD patients with and without depression, including Aβ1-42, p-Tau217, NfL, and HDL-C, which were strongly associated with depressive symptoms. NfL and p-Tau217 emerged as effective predictors of comorbid depression in AD. These results highlight novel biological targets for early diagnosis and personalized treatments, underscoring the importance of multidimensional biomarker assessment in the study of AD with depression. Additional validation should confirm these biomarkers' clinical usefulness.

Disclosure of conflict of interest

None.

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