Invest Clin 66(4): 349 - 364, 2025 https://doi.org/10.54817/IC.v66n4a01

The role of amyloid and tau biomarkers in assessing the effectiveness of drug treatment for Alzheimer's disease.

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Keywords: Amyloid Beta-Peptides; Tau Proteins; Phosphorylated Tau; P-Tau-181, Alzheimer Disease; Drug Therapy.

Abstract. This study aimed to explore the role of amyloid and tau biomarkers in evaluating the effectiveness of drug therapy for Alzheimer's disease (AD). A retrospective analysis was performed in 150 AD patients admitted to our hospital from October 2022 to January 2024, and 50 healthy people were selected as the control group. The basic information of patients, including cognitive function and daily living ability, as well as amyloid and tau biomarkers, was compared between the two groups. AD patients were treated with donepezil hydrochloride and memantine tablets, and were divided into valid and invalid groups based on efficacy. Binary logistic regression analysis was used to identify factors affecting the effectiveness of AD drug treatment, with the predictive accuracy being assessed using ROC curves. This study revealed that compared with the control group, the MMSE (Mini-Mental State Examination), MoCA (Montreal Cognitive Assessment), and Aβ1-42 in the AD group decreased, while T-tau and P-Tau-181 increased ($p<0.05$). Drug treatment was considered effective in 107 out of 150 AD patients. Education years, daily exercise, Aβ1-42, T-tau, and P-Tau-181 are all factors that affect the effectiveness of AD drug treatment. The changes in serum levels of Aβ1-42, T-tau, and P-Tau-181 can all be used to evaluate the effectiveness of AD drug treatment, with AUC values of 0.869, 0.815, and 0.800, respectively. The combined evaluation of the three factors has an AUC of 0.977. Drug therapy can improve the clinical efficacy of most AD patients. The years of education, exercise, Aβ1-42, T-tau and P-Tau-181 are the influencing factors of the efficacy of AD drug treatment. The efficacy of AD drug treatment can be evaluated by detecting the changes of serum Aβ1-42, T-tau and P-Tau-181 levels in clinical practice, and the combined evaluation value of the three is higher than the individual values.

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El papel de los biomarcadores de amiloide y tau en la evaluación de la eficacia del tratamiento farmacológico para la enfermedad de Alzheimer.

Invest Clin 2025; 66 (4): 349 – 364

Palabras clave: Péptidos Beta-Amiloide; Proteínas Tau; Proteína Tau Fosforilada; P-Tau- 181; Enfermedad de Alzheimer; Terapia Farmacológica.

Resumen. El objetivo de este estudio es explorar el papel de los biomarcadores de amiloide y tau en la evaluación de la eficacia de la farmacoterapia para la enfermedad de Alzheimer (EA). Se realizó un análisis retrospectivo de 150 pacientes con EA ingresados en nuestro hospital entre octubre de 2022 y enero de 2024, y se seleccionaron 50 personas sanas como grupo control. Se compararon la información básica, la función cognitiva, la capacidad para realizar las actividades de la vida diaria, así como los biomarcadores de amiloide y tau entre ambos grupos. Los pacientes con EA fueron tratados con tabletas de hidrocloruro de donepezilo y memantina, y se dividieron en un grupo de pacientes que respondieron al tratamiento y otro grupo de pacientes que no respondieron, en función de la eficacia del mismo. Se utilizó un análisis de regresión logística binaria para identificar los factores que afectan la eficacia del tratamiento farmacológico de la EA, y se evaluó la precisión predictiva mediante curvas ROC. Los resultados de este estudio revelan que, en comparación con el grupo control, en el grupo de EA, las puntuaciones en las escalas MMSE, MoCA y los niveles de Aβ1-42 disminuyeron, mientras que los niveles de T-tau y P-Tau-181 aumentaron ($p<0,05$). Después del tratamiento farmacológico, 107 de los 150 pacientes con EA mostraron una respuesta favorable. Los años de educación, el ejercicio diario, los niveles de Aβ1-42, T-tau y P-Tau-181 son todos factores que afectan la eficacia del tratamiento farmacológico de la EA. Los cambios en los niveles séricos de Aβ1-42, T-tau y P-Tau-181 pueden servir para evaluar la eficacia del tratamiento farmacológico de la EA, con valores de área bajo la curva (AUC) de 0,869, 0,815 y 0,800, respectivamente. La evaluación combinada de estos tres factores tiene un AUC de 0,977. La farmacoterapia puede mejorar la eficacia clínica en la mayoría de los pacientes con EA. Los años de educación, el ejercicio, los niveles de Aβ1-42, T-tau y P-Tau-181 son los factores que influyen en la eficacia del tratamiento farmacológico de la EA. La eficacia del tratamiento farmacológico de la EA puede evaluarse detectando los cambios en los niveles séricos de Aβ1-42, T-tau y P-Tau-181 en la práctica clínica. Además, el valor de la evaluación combinada de estos tres biomarcadores es mayor que la evaluación de estos factores individualmente.

Received: 02-07-2025 Accepted: 12-07-2025

INTRODUCTION

Alzheimer's disease (AD) is a degenerative neurological disorder, clinically manifested as memory impairment and irreversible progressive memory loss, among others. In addition, patients may also experience language and visual-spatial disorders, which mainly affect the elderly [1, 2]. With the increase of aging, the incidence rate of AD is increasing year by year, and its impact on the social economy is also increasingly significant [3]. At present, AD is mainly relying on drug treatment supplemented by comprehensive measures such as psychological and cognitive interventions [4]. In terms of drug therapy, cholinesterase inhibitors, glutamate receptor antagonists, and other cognitive enhancement drugs are mainly used [5]. However, due to the complexity and multifactorial nature of AD disease, as well as the challenges faced in evaluating the effectiveness and safety of drugs [6, 7], and that drug therapy can alleviate patients' clinical symptoms, the clinical efficacy is not satisfactory, and additional methods are needed to improve patients' quality of life and cognitive abilities [8, 9]. Therefore, it is necessary to explore biomarkers to evaluate the effectiveness of drugs in order to develop personalized treatment plans tailored to the specific conditions of patients and enhance their clinical efficacy.

Research has shown that the excessive deposition of amyloid-β (Aβ) in cerebral blood vessels and the aggregation of tau protein to form neurofibrillary tangles are the primary pathological mechanisms of AD [10,11]. Aβ is a peptide generated by the amyloid precursor protein (APP) [12, 13], and its primary forms are Aβ1-42 and Aβ1-40, which are important biomarkers in AD [14]. Studies have shown that excessive deposition of Aβ1-42 promotes neuroinflammation, neuronal death and cognitive dysfunction [15]. For mild AD patients, Aβ begins to accumulate abnormally in the early stages of the disease, and soluble Aβ1-42 levels decrease; however, the damage to nerve cells and neural networks is relatively mild at this time. Timely anti-amyloid treatment can effectively prevent the progression of the disease [16]. Tau protein plays a crucial role in maintaining the stability of the microtubule structure, facilitating axonal transport, and regulating neuronal function [17]. However, in AD patients, the abnormal phosphorylation and aggregation of the Tau protein lead to the formation of neurofibrillary tangles, which destroy the cellular structure and trigger neuronal death [18]. Among them, phosphorylated tau protein 181 (P-Tau-181) is a phosphorylated form of T-tau [19]. Under normal circumstances, the content of P-Tau-181 in blood or spinal fluid is minimal. Therefore, detection of P-Tau-181 levels can reflect neural or cognitive function [20].

However, there is currently no report on whether amyloid protein and tau biomarkers can be used to evaluate the effectiveness of drug therapy. Therefore, this study examines the role of serum Aβ1-42, P-Tau-181, and T-tau biomarkers in evaluating the effectiveness of AD drug therapy, aiming to provide personalized treatment plans for patients and thereby improve treatment outcomes, to provide further laboratory evidence for drug treatment and clinical reference for saving patients' lives and improving prognosis.

MATERIALS AND METHODS

Subjects

Regression analysis was conducted on 150 AD patients admitted to our hospital between February 2023 and January 2024. Fifty healthy individuals were included as the control group. Through multidisciplinary consultations in neurology, psychiatry, rehabilitation, and other fields, comprehensive evaluations and confirmations of AD patients were conducted using EEG and head MRI examinations (Fig. 1).

Inclusion criteria: ①Meet the diagnostic criteria for AD [21], age≥55 years; ②Com-

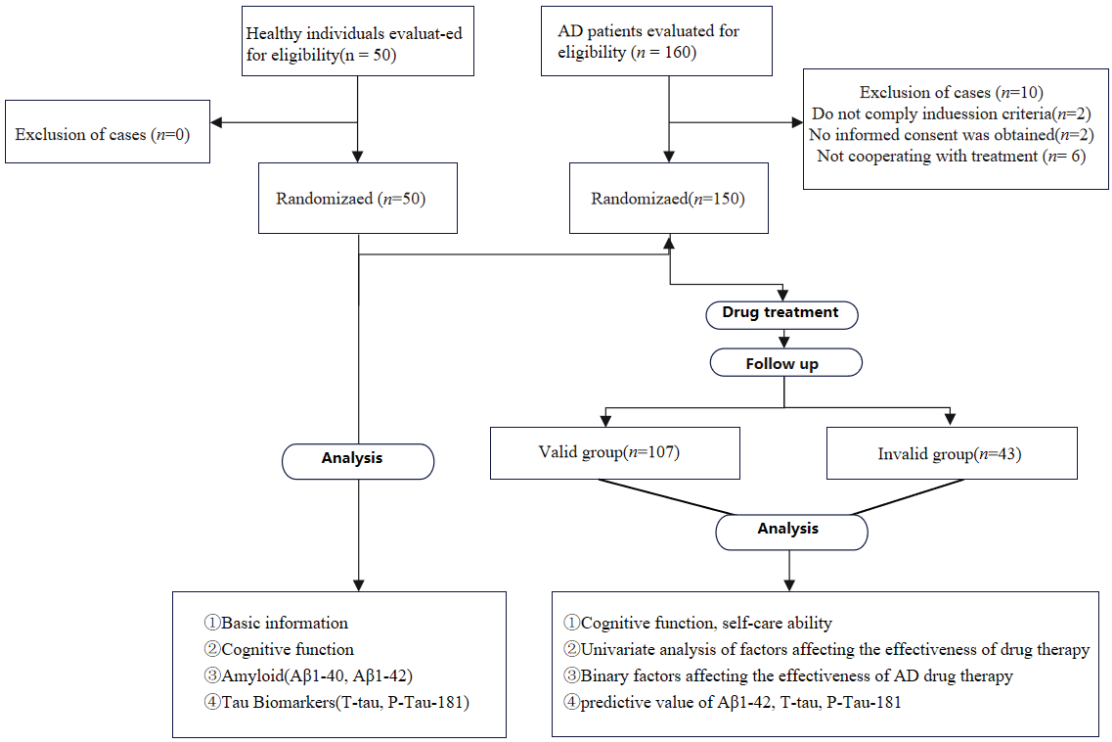

Fig. 1. Study design drawing.

plete clinical data; ③Could communicate fluently in Mandarin, understand the questionnaire content, and complete various survey evaluations; ④Good compliance; ⑤Expected survival period≥6 months; ⑥Tolerate the treatment plan related to this study; ⑦A score of≥27 on the Mini Mental State Examination (MMSE) and/or≥26 on the Montreal Cognitive Assessment Scale (M0CA) for healthy individuals during the same period.

Exclusion criteria: ①Patients with comorbidities of other mental illnesses; ②Long-term use of sedatives and sleeping pills; ③Individuals who are allergic to the medication used in this study; ④Serious infectious diseases of body organs; ⑤Not willing to comply with the follow-up and evaluation plan of this study.

Ethical considerations

This study strictly adheres to the principles of the Declaration of Helsinki, and all research procedures comply with international ethical standards. Has obtained approval from the ethics committee of Shaoxing Seventh People's Hospital. All participants have signed an informed consent form. In emergencies, the consent form may be signed by a representative or guardian of the individual. All data involved in the research process has been anonymized to ensure the privacy and confidentiality of participants' identities.

Therapeutic approaches

All AD patients received drug treatment: oral donepezil hydrochloride (Shaanxi Fangzhou Pharmaceutical Co., Ltd., GYZZ H20030583, specification: 5 mg), one tablet per day. The dose was adjusted four weeks later, the maximum dose was two tablets/per day. if severe insomnia occurred, they were administered in the morning. Oral administration of Meijingang tablets (Hangzhou Baishan Technology Co., Ltd., national drug approval number H20213931, specifi-

cation: 5mg), one tablet/per day, increasing by one tablet/per day per week, the maximum dose was four tablets/per day. Regular monitoring of the patient's blood pressure and provision of medication guidance and education was carried out during nursing. Appropriate sleep schedules were arranged to ensure adequate sleep. The diet was guided to be light, to avoid overeating, stimulating foods, and smoking and alcohol consumption. Moreover, specific psychological counselling was provided, tailored to the patient's situation and treatment for three months.

Detection of indicators

Clinical data: Relevant indicators and clinical data of patients were collected within 24 hours after admission, including gender, age, BMI, clinical symptoms, imaging data, and relevant laboratory examination indicators, as well as basic diseases. Using an electronic blood pressure measuring device (model: HEM-7124, Manufacturer: Omron Company), systolic and diastolic blood pressure values were recorded. Five mL of venous blood was extracted from the patient, the serum separated and an automated chemical analyzer used to detect blood calcium, fasting blood glucose, homocysteine (Hcy), and creatinine (Cr), Urea (BUN), total cholesterol (TC), triglycerides (TG), low-density and high-density lipoprotein cholesterol (LDL, HDL). Jinan Xinrun Medical Equipment Co., Ltd, provided the instruments and supporting reagent kits. The ELISA method was used to detect serum neuregulin1 (NRGl) and Klotho protein. The kit was purchased from Tinglai Biological Company with item number J19117 and validated by at least two intermediate-level pathologists. If there was any objection, the result was reviewed and confirmed by a physician with a senior professional title or above to ensure the reliability of the results.

Cognitive function: Evaluated with the MMSE test (Mini-Mental State Examination)[22], with 1 point for correct answers and 0 point for incorrect answers. The score is proportional to cognitive function. Scores higher than 26 indicate normal cognition. At least one day later, the MoCA test [23] was performed, which covers eight cognitive domains related to visual spatial execution ability, naming, memory, abstract thinking, etc. Scores above 25 indicate normal cognitive. The total score for both tables is 30 points.

Daily living ability: The AD Patient Activities of Daily Living Cooperative Study Scale (ADCS-ADL) was used to evaluate it[24]. The scale encompasses Basic Activities of Daily Living (BADL) and Instrumental Activities of Daily Living (IADL). The BADL section evaluates more basic activities such as dressing, eating, and toileting. The IADL section encompasses complex daily or social activities, such as visiting, working, and performing household chores, that require more cognitive function. The total score is 22 and 56 points. The lower the score, the lower the activity ability.

Amyloid and Tau biomarkers: venous blood was collected from all participants on an empty stomach and measured in real-time using an ELISA method according to diagnosis and treatment needs. The kit was purchased from Fujirebio Corporation in Japan and operated strictly according to the kit instructions.

Follow-up

After three months of drug treatment, a clinical efficacy evaluation was conducted on 150 patients [25], who were divided into three groups: significantly effective (with basic recovery of mental symptoms, complete orientation, MMSE and MoCA scores increased by≥4 points, and self-care ability); effective (with improvement of main mental symptoms, basic orientation, MMSE and MoCA scores increased by 1-3 points, slightly delayed response, and basic self-care ability); and ineffective (not meeting the above criteria). The significant and effective were included in the valid group, and the ineffective in the invalid group.

Outcome measures

Clinical data, cognitive function, and biomarker levels (amyloid and tau) were compared between AD patients and healthy individuals. The effectiveness of drug therapy compared the indicators of cognitive and self-care abilities between the effective and ineffective treatment groups. Factors influencing the effectiveness of drug therapy were evaluated by determining the values of serum Aβ1-42, T-tau, and P-Tau-181 levels in predicting the effectiveness of drug therapy in AD patients.

Statistical analysis

SPSS25.0 software package was used to analyze the data; the count data were expressed as an example (%), and the chi-square test was applied. Measurement data were presented as mean ± SD ($\bar{x}\pm s$), and a t-test was conducted. An ROC curve was constructed, and the corresponding AUC was computed to assess the effectiveness of drug therapy in AD patients. $p<0.05$ was considered statistically significant.

RESULTS

Baseline data

No statistical difference was observed in the baseline characteristics between the two groups ($p>0.05$, Table 1).

Cognitive function and biological indicators

The AD group exhibited decreased MMSE, MoCA, and Aβ1-42 levels, as well as increased T-tau and p-tau-181 levels, compared to the control group ($p<0.05$, Table 2).

Clinical efficacy

After three months of drug treatment, among the 150 AD patients, significant effective, effective and ineffective cases were 62, 45 and 43 cases, respectively, so 107 cas-

Table 1. Baseline comparison between Alzheimer's Disease patients and controls.

Group	*n*	Age (years)	Gender		BMI (kg/m²)	Years of Education (years)
			Male	Female		
Control group	50	66.30±6.08**	24 *(48.00)	*26 (52.00)	23.24±1.10**	9.04±2.99**
AD group	150	65.45±5.81**	*91 (60.67)	*59 (39.33)	23.53±1.76**	9.22±4.08**
t/χ2-value		-0.890	2.462		1.362	0.334
p-value		0.375	0.117		0.175	0.739

AD: Alzheimer's Disease; BMI: Body Mass Index. The data is presented as * n (%), or** mean ± SD

Table 2. Comparison of indicators between Alzheimer's Disease and control groups.

Group	*n*	MMSE	MoCA	Aβ1-40	Aβ1-42	T-tau	P-Tau-181
Control group	50	28.50±0.99	27.74±0.83	317.79±17.38	188.66±17.77	461.68±26.01	49.77±6.48
AD group	150	12.50±1.65	11.51±1.71	322.89±31.29	163.76±26.03	497.59±46.13	62.11±12.67
t-value		-82.144	-89.167	1.439	-7.567	6.746	8.929
p		<0.001	<0.001	0.152	<0.001	<0.001	<0.001

Abbreviations: AD: Alzheimer's Disease; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; Aβ1-40: Amyloid-beta 1-40; Aβ1-42: Amyloid-beta 1-42; T-tau: Total tau protein; P-Tau-181: Phosphorylated tau protein at threonine 181. Data Expression: The data is presented as mean ± standard deviation (SD).

Table 3. Comparison of MMSE, MoCA, BADL, IADL between valid and invalid groups.

Group	*n*	MMSE		MoCA	
		Before treatment	After treatment	Before treatment	After treatment
Valid group	107	12.44±1.67	20.33±5.20*	11.59±1.79	19.26±4.81*
Invalid group	43	12.65±1.60	12.21±2.65	11.33±1.49	11.05±2.47
t-value		-0.710	12.580	0.854	13.735
p		0.471	<0.001	0.395	<0.001

Group	*n*	BADL		IADL	
		Before treatment	After treatment	Before treatment	After treatment
Valid group	107	8.32±1.47	16.43±3.06*	18.71±1.41	29.56±5.56*
Invalid group	43	8.16±1.79	9.28±1.32*	19.02±1.54	21.35±2.40*
t-value		0.505	19.996	-1.200	12.625
p value		0.616	<0.001	0.232	<0.001

Compared with before the treatment, *p<0.05.

Abbreviations: AD: Alzheimer's Disease; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; BADL: Basic Activities of Daily Living; IADL: Instrumental Activities of Daily Living. Data Expression: The data is presented as mean ± standard deviation (SD).

es were included in the valid group, accounting for 71.33%. There were 43 cases in the invalid group, accounting for 28.67%.

Cognitive function and self-care ability

The MMSE, MoCA, BADL, and IADL scores of the valid group were higher than those of the invalid group ($p<0.05$, Table 3).

Univariate analysis of factors affecting the effectiveness of drug therapy in AD

Compared with the invalid group, the valid group had longer years of education, engaged in daily exercise, had higher levels of Aβ1-42, and lower levels of T-tau and P-Tau-181 ($p<0.05$, Table 4).

Logistic regression analysis of factors influencing the effectiveness of AD drug therapy

Analyzing the statistically significant factors in univariate analysis, with the effectiveness of AD drug treatment as the dependent variable (effectiveness=0, ineffectiveness=1), education years (actual value), daily exercise (yes=1, no=0), Aβ1-42 (actual value), T-tau (actual value), P-Tau-181 (actual value) as independent variables, binary logistic regression analysis was conducted. The results showed that education years, daily exercise, Aβ1-42, T-tau, and P-Tau-181 were all factors affecting the effectiveness of AD drug treatment ($p<0.05$, Table 5).

The predictive value of Aβ1-42, T-tau, P-Tau-181 in AD drug therapy

The AUC values for predicting the efficacy of AD drug treatment using serum Aβ1-42, T-tau, and P-Tau-181 levels were 0.869, 0.815, and 0.800, respectively, with cut-off values of 154.67 (ng/L), 517.95 (ng/L), and 63.66 (ng/L). The sensitivities were 76.74%, 69.77%, and 72.09%, respectively, and the specificities were 83.18%, 81.31%, and 71.03%. The AUC of the joint prediction of the three factors is 0.954, with a cut-off value of 0.292, a sensitivity of 90.70%, and a specificity of 93.46%, See Fig. 2 and Table 6.

Table 4. Univariate analysis of factors affecting the effectiveness of drug therapy in Alzheimer's disease patients.

Factors	n	Valid group (n=107)	Invalid group (n=43)	t/χ^2-value	*p*
Age (years)		65.30±5.97	65.81±5.43	-0.490	0.625
Gender					
Male	91	68 (63.55)	23 (53.49)		
Female	59	39 (66.45)	20 (46.51)		
Duration of disease (years)		3.14±0.44	3.23±0.57	-0.952	0.345
BMI (kg/m^2)		23.51±1.76	23.59±1.78	-0.247	0.805
Systolic pressure (mmHg)		130.04±16.01	128.81±12.28	0.450	0.653
Diastolic pressure (mmHg)		79.21±8.08	79.51±10.48	-0.167	0.868
Years of Education (years)		10.93±3.82	4.95±2.42	12.298	<0.001
Drinking					
Yes	109	80 (74.77)	29 (67.44)	2.511	0.113
No	41	27 (25.23)	14 (32.56)		
Family history					
Yes	15	10 (9.35)	5 (11.63)	0.177	0.674
No	135	97 (90.65)	38 (88.37)		
Diabetes					
Yes	34	21 (19.63)	13 (30.23)	1.969	0.161
No	116	86 (80.37)	30 (69.77)		
Hyperlipidemia					
Yes	50	32 (29.91)	18 (41.86)	1.972	0.160
No	100	75 (70.09)	25 (58.14)		
Marital status					
Married	117	87 (81.31)	30 (69.77)	2.381	0.123
Other	33	20 (18.69)	13 (30.23)		
Daily exercise					
Yes	100	85 (79.44)	15 (34.88)	27.402	<0.001
No	50	22 (20.56)	28 (65.12)		
Blood calcium (mmol/L)		2.28±0.17	2.32±0.14	-1.499	0.136
Fasting blood glucose (mmol/L)		4.95±1.01	4.98±0.79	-0.144	0.886
Hcy (μmol/L)		17.72±3.11	17.96±2.90	-0.436	0.664
Cr (μmol/L)		57.66±6.31	57.73±4.60	-0.073	0.942
BUN (mmol/L)		5.38±1.28	5.28±0.89	0.551	0.582
TC (mmol/L)		4.92±1.04	4.97±0.69	-0.382	0.703
TG (mmol/L)		1.28±0.18	1.30±0.20	-0.557	0.579

Table 4. CONTINUATION

Factors	n	Valid group (n=107)	Invalid group (n=43)	t/χ^2-value	*p*
LDL (mmol/L)		2.75±0.32	2.76±0.39	-0.289	0.773
HDL (mmol/L)		1.26±0.14	1.27±0.10	-0.352	0.726
NRGl (ng/L)		340.62±27.22	332.20±30.48	1.665	0.100
Aβ1-40 (ng/L)		321.83±29.51	325.53±35.56	-0.653	0.515
Aβ1-42 (ng/L)		173.90±24.76	138.50±24.76	8.464	<0.001
T-tau (ng/L)		483.43±41.57	532.83±37.49	12.298	<0.001
P-Tau-181 (ng/L)		57.97±9.96	72.41±12.91	-6.590	<0.001

Abbreviations: BMI: Body Mass Index; Hcy: Homocysteine; Cr: Creatinine; BUN: Blood Urea Nitrogen; TC: Total Cholesterol; TG: Triglycerides; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; NRGl: Neurogranin; Aβ1-40: Amyloid-beta 1-40; Aβ1-42: Amyloid-beta 1-42; T-tau: Total tau protein; P-Tau-181: Phosphorylated tau protein at threonine 181. Data Expression: The data is presented as mean ± standard deviation (SD) or n(%).

Table 5. Logistic regression analysis of factors influencing the efficacy of drug treatment in Alzheimer's disease patients.

Factors	B	SE	Wald/χ2	p	OR	95%CI
Years of Education	-0.487	0.146	11.125	0.001	0.614	0.461-0.818
Daily exercise	-2.148	0.939	5.235	0.022	0.117	0.019-0.735
Aβ1-42	-0.065	0.022	8.400	0.004	0.937	0.897-0.979
T-tau	0.032	0.012	7.841	0.005	1.033	1.010-1.056
P-Tau-181	0.107	0.039	7.691	0.006	1.113	1.032-1.200

Abbreviations: AD: Alzheimer's Disease; B: Regression Coefficient; SE: Standard Error; OR: Odds Ratio; 95% CI: 95% Confidence Interval; Aβ1-42: Amyloid-beta 1-42; T-tau: Total Tau Protein; P-Tau-181: Phosphorylated Tau Protein at Threonine 181.

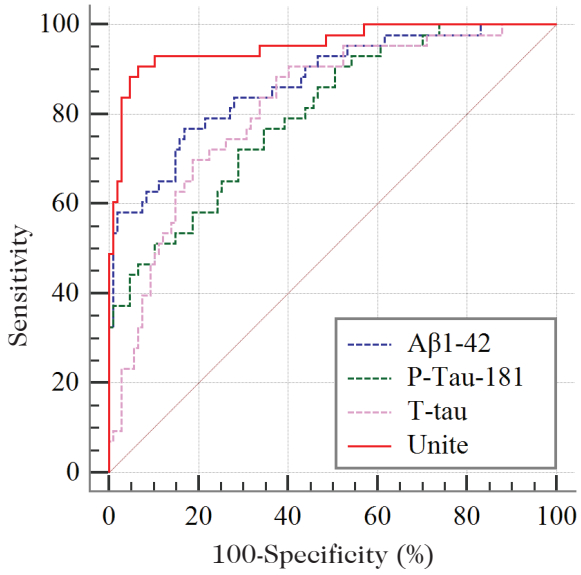

Fig. 2. ROC curves for predicting the therapeutic effect of AD drugs using Aβ1-42, T-tau, P-Tau-181.

Table 6. Diagnostic Value of A β1-42, T-tau, P-Tau-181 in the Efficacy of Alzheimer's disease drug therapy.

Indicators	AUC	p	Best Cut-off Value	Sensitivity (%)	Specificity (%)	95% CI
Aβ1-42	0.869	<0.001	154.67	76.74	83.18	0.805-0.919
T-tau	0.815	<0.001	517.95	69.77	81.31	0.743-0.874
P-tau-181	0.800	<0.001	63.66	72.09	71.03	0.727-0.861
Unite	0.954	<0.001	0.292	90.70	93.46	0.908-0.982

Abbreviations: AUC: Area Under the Curve; 95% CI: 95% Confidence Interval; Aβ1-42: Amyloid-beta 1-42; T-tau: Total Tau Protein; P-Tau-181: Phosphorylated Tau Protein at Threonine 181.

DISCUSSION

AD is a global public health and social care issue, with 10 million AD patients in China [26], and the patient population is becoming younger. Early prevention and treatment, as well as improving the effectiveness and safety of drug therapy, are important means to delay disease progression and enhance quality of life. Aβ1-42 is a protein fragment produced by enzymatic hydrolysis of APP, which can be used as an effective indicator of cognitive function [27]. Tau protein can stabilize microtubules in nerve cells and is closely associated with cognitive impairment[28]. Relevant studies have shown [29, 30], that the Aβ1-42, T-tau and P-tau-181 proteins can be used to evaluate the occurrence of cognitive impairment in AD patients. Compared with healthy individuals, serum Aβ1-42 levels are decreased, and T-tau and P-Tau-181 levels are increased in AD patients, which is consistent with the results of this study. This suggests that the changes in the above proteins can serve as potential biomarkers for predicting AD patients. However, there is currently no report on whether they can evaluate the effectiveness of drug therapy in AD patients.

This study demonstrated effective clinical efficacy in 107 of 150 AD patients (71.33%) after three months of drug treatment, while in 43 cases, it was ineffective, accounting for 28.67%. The MMSE, MoCA, BADL, and IADL scores of the valid group were higher than those of the invalid group. This suggests that donepezil hydrochloride and memantine tablets can enhance the efficacy, cognitive function, and self-care abilities of most patients. It is speculated that donepezil hydrochloride is an acetylcholinesterase inhibitor, which increases the concentration of acetylcholine by inhibiting its activity and reducing its breakdown, thereby improving patients' cognitive function and neurotransmission function [31]. Moreover, this process is reversible and can help stabilize the level of acetylcholine in the body[32]. Meijingang tablets are a non-competitive NMDA antagonist that can reduce neurotoxicity by blocking excessive glutamate activation of NMDA receptors, thereby protecting neurons and enhancing cognitive function[33]. The combination of the two can exert a synergistic effect, further improving the clinical efficacy, cognitive function, and self-care ability of AD patients. However, there are still a few patients with unsatisfactory treatment outcomes. Therefore, we need to explore further the factors that affect the effectiveness of drug therapy, such as education level, physical activity, and severity of the disease, so that the medical staff can adjust the dosage and type of drugs according to the patient's condition on time, in order to improve the efficacy of drug treatment.

Logistic regression analysis showed that education years, daily exercise, Aβ1-42, T-tau, and P-Tau-181 are influencing factors on the effectiveness of AD drug treatment. It is speculated that this may be because the length of education is closely related to the cognitive reserve of the brain, which is the

brain's ability to maintain cognitive abilities by activating and utilizing previously experienced neural networks, and serves as a resource for processing information and solving problems [34]. Patients with longer educational years are tipically able to accumulate more knowledge and problem-solving skills, have higher cognitive reserves, maintain higher treatment compliance when facing treatment, better understand the importance of medication treatment, and take medication according to medical orders, thereby improving treatment effectiveness[35]. Furthermore, patients with higher education are more likely to seek ways to obtain support from their families and society [36], and to receive more help and encouragement during the treatment process. Patients with lower education may have poorer cognitive function and self-care abilities, lack understanding of the disease, have greater disease uncertainty, and thus lack attention and cooperation in treatment, which affects treatment efficacy [37]. Daily exercise is considered an important non-pharmacological intervention that can improve brain health, enhance neuroplasticity, promote blood circulation, increase oxygen supply to the brain [38], enhance muscle strength, and improve cardiovascular function. It helps dementia patients maintain good physical fitness, reduce functional decline caused by physical reasons, and improve functional outcomes. Exercise also promotes the recovery of the endocrine and immune system function [39], and helps reduce AD-related pathological processes such as inflammation and oxidative stress, improving clinical outcomes. Studies have shown that for AD patients receiving medication treatment, regular physical exercise can not only alleviate potential side effects such as fatigue and depression caused by medication, but also improve patients' compliance with treatment. For example, dance, as a physical and mental exercise method, emphasizes calmness and relaxation during movement, and requires concentration to achieve a harmonious unity of consciousness and movement, thereby achieving the effects of physical and mental balance and spiritual relaxation [40]. In addition, exercise can enhance dopamine binding ability in the brain, delay neurodegenerative changes, delay memory decline symptoms, and regulate the secretion of neurotransmitters such as norepinephrine. This can promote memory recovery and enhance sensory input, reaction speed, and other cognitive functions, thereby achieving cognitive improvement [41]. In addition, exercise can reduce NLRP3 inflammation and improve the redox balance, which together slow the progression of AD[42]. Therefore, higher education levels and daily exercise are factors that affect the effectiveness of AD drug treatment.

Aβ deposition is one of the pathological changes in AD, which can easily cause neurotoxicity, inflammatory reactions, etc., leading to neuronal dysfunction, death, and other phenomena [43]. Moreover, Aβ1-42 is a protein fragment produced by enzymatic hydrolysis of APP, the abnormal processing of APP in AD patients reduces the production of soluble Aβ1-42, leading to neuroinflammation and neuronal damage, including interference with nerve signal transmission, triggering inflammatory reactions, damaging the stability of neurons and synaptic connections, ultimately resulting in pathological changes and degenerative damage to the nervous system, causing cognitive impairment and other symptoms [44]. The reduction of Aβ1-42 may also affect the pathological state of other key molecules, such as the Tau protein, further accelerating disease progression. In addition, the reduction of Aβ1-42 also inhibits the activity of gamma-secretase, thereby reducing the clearance of Aβ deposition and forming a vicious cycle[45]. Under normal circumstances, tau protein maintains the stability and function of neuronal microtubules [46]. However, in AD, the T-tau protein undergoes excessive phosphorylation, transforming it from a microtubule-binding protein to the primary component of neurofibrillary tangles,

which in turn causes neuronal degeneration and cognitive dysfunction. P-Tau-181, a phosphorylated T-tau form, exhibits neurotoxicity, promoting neuronal death and dysfunction, thus impacting AD progression [47]. Therefore, low serum Aβ1-42 levels and high levels of T-tau and P-Tau-181 in patients can affect the effectiveness of drug treatment. Consequently, we speculate that the effectiveness of drug therapy can be evaluated by monitoring changes in the levels of the three factors. This study confirmed through ROC curve analysis that the level changes of the three have a good assessment value, and the value of joint analysis of the three is higher. The reason may be that they each play unique and complementary roles in the pathogenesis of AD patients, and together affect cognitive function and drug efficacy. Combined detection provides a more comprehensive reflection of the effectiveness of drug treatment in patients, thereby improving their predictive value.

Although this study analyzed clinical data from AD patients and explored early predictors of the effectiveness of drug therapy, it has some limitations. This study is a retrospective analysis with a small sample size and a relatively short follow-up period of only three months. While this duration was sufficient to observe initial treatment responses, it is important to note that AD is a chronic and progressive condition. A more extended follow-up period would be essential to fully capture the dynamic changes in β-amyloid and tau protein levels, as well as to better understand the long-term effectiveness and potential side effects of the drug therapy. Future research should focus on prospective studies with larger sample sizes and extended treatment cycles to improve the reliability and applicability of the results.

Additionally, the potential heterogeneity of the patient sample is another limitation. This study did not stratify patients based on the stage of disease progression, which could influence the observed treatment responses and biomarker levels. Patients with AD at different stages may exhibit varying degrees of cognitive impairment, biomarker profiles, and treatment efficacy. Therefore, it is crucial to consider the disease stage when interpreting the results and to conduct stratified analyses in future studies to account for this variability. In the future, a comprehensive evaluation should be conducted based on the influence of multiple biomarkers and pathological mechanisms. Moreover, a detailed assessment considering factors such as clinical manifestations, genetic background, and disease severity of patients should be performed to meet the treatment needs of AD patients and to develop more personalized therapeutic strategies.

In conclusion, donepezil hydrochloride combined with memantine tablets can improve the clinical efficacy, function and self-care ability of most patients with AD. However, the efficacy of treatment is not ideal for some patients. Several factors influence the effectiveness of Alzheimer's disease (AD) drug therapy, including years of education, daily exercise, and biomarkers such as Aβ1-42, T-tau, and P-Tau-181. In clinical practice, the effectiveness of AD drug treatment can be assessed by monitoring changes in the levels of these three factors. Additionally, a combined evaluation of all three factors provides a more comprehensive assessment of treatment outcomes.

Acknowledgment

None.

Funding

To explore the mechanism of the NLRP3caspase-1GSDMD pathway mediated by miR-146a-5p to regulate the progression of Alzheimer's disease based on the inflammatory microenvironment (No. 2023A14029).

Study on the mechanism of regulating microglia mitochondria autophagy of

Ginseng Yangrong Decoction to improve cognitive ability of Alzheimer's disease (No. 2024ZL1138).

Conflicts of interest

The authors declare that they have no financial conflicts of interest.

Consent to publish

The manuscript has neither been previously published nor is it under consideration by any other journal. The authors have all approved the content of the paper.

Consent to participate

We secured a signed informed consent form from every participant.

Ethic approval

This experiment was approved by the Shaoxing Seventh People's Hospital Ethics Committee.

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Author participation

JS: Developed and planned the study, performed experiments, and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions. YL, JC: Participated in collecting, assessing, and interpreting the data. Made significant contributions to date interpretation and manuscript preparation. MZ: Provided substantial intellectual input during the drafting and revision of the manuscript.

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