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ORIGINAL ARTICLE

Factors associated with cognitive function in patient with Alzheimer's disease with newly prescribed acetylcholinesterase inhibitors: A 1-year retrospective cohort study

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Abstract

Objective: We aimed to examine the factors associated with treatment outcomes in patients with Alzheimer's disease (AD) after 1 year of acetylcholinesterase inhibitors (AChEI) treatment.

Method: We obtained electronic medical records from a medical center in Southern Taiwan between January 2015 and September 2021. Participants aged ≥60 who were newly diagnosed with AD and had been prescribed AChEIs were included. Cognitive assessments were performed before the AChEIs were prescribed and at the 1 year follow-up. Cognition progressors were defined as a Mini-Mental State Examination decline of >3 or a Clinical Dementia Rating decline of ≥1 after 1 year of AChEI treatment. The relationship between the baseline characteristics and cognitive status after follow-up was investigated using logistic regression analysis after adjusting for potential confounders.

Results: A total of 1370 patients were included in our study (mean age, 79.86 ± 8.14 years). After adjustment, the body mass index (BMI) was found to be significantly lower in the progressor group [adjusted odds ratio (AOR): 0.970, 95% confidence intervals (95% CIs): 0.943 to 0.997, $P = 0.033$]. The usage of antipsychotics was significantly higher in the progressor group (AOR: 1.599, 95% CIs: 1.202 to 2.202, $P = 0.001$). The usage of benzodiazepine receptor agonists also tended to be significantly higher in the progressor group (AOR: 1.290, 95% CIs: 0.996 to 1.697, $p = 0.054$).

Conclusion: These results suggest that patients with AD who receive 1 year of AChEI treatment and have a lower BMI or concurrent treatment with antipsychotics and benzodiazepine receptor agonists are more likely to suffer from cognitive decline.

KEYWORDS
acetylcholinesterase inhibitors, Alzheimer's disease, antipsychotic, cognitive function, dementia, retrospective study

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1 | INTRODUCTION

About 55 million people worldwide were estimated to have dementia in 2020.[1] Alzheimer's disease (AD) is the most common cause of dementia and accounts for approximately 75% of patients with dementia.[2] AD is a multifactorial disease, and its progression of disease status involves several mechanisms arising from the interactions of multiple factors. Increasing age, psychiatric comorbidities such as depression, chronic physical conditions including diabetes, arterial hypertension, hypercholesterolemia, cerebrovascular disease, and lifestyle are the strongest risk factors.[3] The most studied factors associate with accelerate disease progression include age at disease onset, sex, education, clinical features, genotype, comorbidities, and antidementia therapies.[4] One study considered antidementia therapy a strong confounding factor, as 84.4% of the participants had received either acetylcholinesterase inhibitors (AChEIs), memantine, or both. The authors felt that this factor might explain why the majority of the recruited patients (61.9%) exhibited slow cognitive decline.[5]

AChEIs have proven beneficial for relieving symptoms and have been clinically used for the treatment of AD in many countries for decades.[6] Currently, the hypothesis of cholinergic neurotransmission remains the primary approach in AD treatment. AchEIs increase the concentration of acetylcholine in the temporal lobe and hippocampus by inhibit its degradation. As a result they slow the cognitive decline in AD patients.[7] Past studies on AChEIs have been mainly randomized clinical trials (RCTs) in which those who received an AChEI and those who received a placebo had their cognitive function compared.[8] Such a design ensures the identification of treatment efficacy but cannot assess heterogeneity among individuals receiving AChEIs.[9] A retrospective cohort study that investigated the predictors of different cognitive trajectories included 2460 patients who had been prescribed AChEIs. The results showed that the reduced Mini-Mental State Examination (MMSE) score after AChEI administration was significantly associated with non-white ethnicity, nonvascular events, and the absence of antipsychotics and anticoagulants.[10] This study showed that, aside from the presentation of AChEI treatment, several factors appear to be associated with the treatment response of patients. Therefore, an observational study investigating heterogeneity in the treatment effect of AChEIs within a large population with generalizable characteristics is warranted.[11]

The behavioral and psychological symptoms of dementia (BPSD) have long been identified as association with poor outcomes for patients with AD and also appeared to have higher incidence when disease progressed.[12] The high incidence of BPSD has led to numerous patients with AD been prescribed of antipsychotics, antidepressants, and analgesics.[13] However, in the 2019 Beers Consensus Criteria for safe medication use in the elderly, they recommended avoiding antipsychotics and sedative agents in patients with dementia due to their increased risk of mortality, and cognitive function exacerbation.[14] Previous studies have mainly focused on the effects of AChEIs in the treatment of BPSD and how they can reduce the use of antipsychotics and antidepressants.[15–17] Few studies have examined the effects of antipsychotics, antidepressants, and analgesics on the treatment effects of AChEIs in patients with AD. The data for clinical treatment effect of AChEIs in AD with BPSD that require the treatment of psychiatric medication still showed heterogenous results.[18] As for the high prevalence usage of the psychiatric medication in clinical AD patient, we aim to investigate the effect of their usage on AChEIs treatment.

In response to the abovementioned issues, we conducted this retrospective cohort study which focuses on the predisposing and precipitating factors that could impact the cognitive function preservation effect of AChEIs in patients with AD from East Asia.

2 | METHODS

2.1 | Data source and data availability

We obtained electronic medical records from Kaohsiung Veterans General Hospital (KSVGH), a medical center in Southern Taiwan, between January 2015 and September 2021. The KSVGH data used the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) for diagnosis. This study was partly based on data from the Department of Medical Education and Research and the Research Center of Medical Informatics at Kaohsiung Veterans General Hospital. The interpretation and conclusions contained herein do not represent the position of Kaohsiung Veterans General Hospital.

2.2 | Study population and the study design

In Taiwan, blood analyses, brain imaging, and cognitive assessments must be performed before antidementia medications can be prescribed. Furthermore, patients undergo cognitive assessments (MMSE, Clinical Dementia Rating Scale [CDR], or Cognitive Abilities Screening Instrument [CASI]) once a year to confirm the efficacy of their antidementia medication.[19–21] We enrolled participants aged ≥60 who were newly diagnosed with AD (ICD-10-CM code: G30) and had been prescribed an AChEI (donepezil, rivastigmine, and galantamine) by a board-certified psychiatrist or neurologist. The AD was diagnosed by psychiatrist or neurologist in both outpatient and in patient settings in our hospital and documented on the medical records. The diagnosis was based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition(DSM-V) with evidence of clinical signs or psychological evaluation that was documented in the medical records. The medical records were reviewed by two of our authors to ensure the validity. Patients with stroke, brain tumors, or brain injury were excluded based on brain imaging reports. We also excluded patients with schizophrenia spectrum disorder (ICD-10-CM: F20.0 ~ F20.9), bipolar spectrum disorder (F31.0 ~ F31.9), epilepsy (ICD-10-CM: G40), organic disorders (ICD-10-CM: F06), liver cirrhosis or liver failure (ICD-10-CM: K70.3, K70.4, K71, K72, K74.3, K74.4, K74.5, and K74.6), end-stage renal disease (ICD-10-CM:

N18.6), and thyroid disorders (ICD-10-CM: E00-E07). Patients with AD were requested to continue on the same AChEI for 1 year and undergo a cognitive assessment 1 year after their first prescription. Therefore, each participant underwent two assessments (baseline just before AChEI treatment and 1 year after AChEI treatment). Cognition progressors were defined as an MMSE decline of >3 or a CDR decline of >1 in a single year.

Demographic data, including the age (date of first AChEI prescription), sex, education (years), place of residence (living with family, alone, or institution), height, weight, and the body mass index (BMI), were collected. The latest laboratory data within the year prior to the AChEI being prescribed was obtained, including the level of creatine (CRE), aspartate aminotransferase (AST), alanine aminotransferase (ALT), thyroid stimulating hormone, free thyroxine (T4), triiodothyronine (T3), vitamin B12, folate, glycated hemoglobin (HbA1c), hemoglobin (Hb), triglyceride (TG), low-density lipoprotein cholesterol (LDL), and total lipoprotein cholesterol (CHOL). Physical comorbidities were defined using the ICD-10-CM code and medical record given by a physician before the first AChEI prescription in the database or based on the latest laboratory data as follows: Arterial hypertension: (ICD-10-CM: I10), diabetes mellitus: (ICD-10-CM: E10, E11), dyslipidemia: (ICD-10-CM: E78), chronic kidney disease: (ICD-10-CM:N18.3, N18.4, N18.5, N18.6), and coronary artery disease: (ICD-10-CM: F32, F33, F34.1, F34.89). Subcortical arteriosclerotic encephalopathy (SAE) was defined using brain imaging such as *Magnetic Resonance Imaging or* Computed Tomography (yes or no). Medication exposure to benzodiazepine receptor agonists (BZRA), antidepressants, and antipsychotics was determined based on whether they had been prescribed (yes or no) before the date of the first AChEI prescription. Cognitive assessments were performed before the AChEI prescription and 1 year later. We extracted the MMSE score, CDR score, CDR box (sum of the scores of each domain), CASI score, and the score of each domain of the CASI.

2.3 | Data analysis

The Bonferroni correction was utilized to adjust the significance thresholds for multiple comparisons, thereby controlling the family-wise error rate. The *p*-value threshold was adjusted by dividing the conventional alpha level of 0.05 by the number of comparisons performed (number of comparisons = 26). We employed logistic regression analysis to explore the factors potentially associated with faster cognitive decline. The choice of logistic regression was driven by the binary nature of the outcome variable (progressor vs. nonprogressor). The variables in the model would selected based on prior research indicating their relevance to cognitive decline.

3 | RESULTS

A total of 1370 patients were included in our study (mean age, 79.86 ± 8.14 years). The characteristics of the progressor and nonprogressor groups are shown in Table 1. Among them, 50.2% were male, 77.9% lived at home, and 19.2% lived in institutions (Table 1). A total of 27 comparisons were performed. According to Bonferroni correction, when the *p*-value is less than 0.002, it is considered to have a statistically significant difference. As for demographic data, there were no significant difference in the sex, age, education, and the BMI between the two groups (Table 1). There were no significant differences in the initial cognitive function assessment between the two groups. No significant differences were found in terms of physical comorbidities including SAE, diabetes mellitus, arterial hypertension, coronary artery disease, dyslipidemia, chronic kidney disease, anemia, liver function, thyroid function, or vitamin B12 and folate concentrations. The progressor group had a higher prevalence of antipsychotics prescription than the nonprogressor group (antipsychotics: 25.2% vs. 16.5%, $p < 0.001$). No statistically significant differences were observed in the combined use of BZRA and antidepressants (Table 1). The prescription of different types of AChEIs also showed no significant difference between progressor and nonprogressor group.

The differences between the baseline and 1-year follow-up cognitive function assessments among the nonprogressor and progressor groups are shown in Table 2. Significant differences were found in the MMSE (−6.172, 95% CIs: −6.509 to 5.836), CDR (0.428, 95% CIs: 0.379 to 0.477), CDR box (2.231, 95% CIs: 1.984 to 2.478), and CASI (−14.798, 95% CIs: −15.906 to −13.690) scores between the nonprogressor and progressor groups. In the categories of CASI, the largest differences were found in the orientation sub-domain (−3.091, 95% CIs: −3.455 to −2.727).

Table 3 summarizes the factors associated with faster cognitive decline in the progressor group after 1 year of AChEI treatment after adjusting for potential confounding factors. We selected basic demographics (age and sex), types of AChEI, antipsychotics use, BZRA use, BMI, and CDR box as potential parameters. Lower BMI (adjusted odds ratio [AOR]: 0.970, 95% CIs: 0.943 to 0.997) and combined usage of antipsychotics [(AOR): 1.599, 95% CIs: 1.202 to 2.128] were found to be significant factors that associate with faster cognitive decline. Combined use of BZRA also showed a trend toward significance ([AOR]: 1.290, 95% CIs: 0.996 to 1.672).

4 | DISCUSSION

The present study aimed to explore the factors associated with changes in cognitive function after 1 year of AChEI treatment. The main findings were as follows: (1) patients with a lower baseline BMI exhibited a higher risk of cognitive decline after 1 year of AChEI treatment compared to those with a higher baseline BMI; (2) the concurrent use of antipsychotics in patients was associated with an increased risk of disease progression; and (3) concurrent usage of BZRA in patients with AD showed a significant trend with cognitive worsening.

The first finding of the present study was that patients with AD with a lower baseline BMI were more likely to experience cognitive

TABLE 1 Group comparisons of baseline characteristics and other covariables between progressors and nonprogressors.

	Nonprogressor ($n=854$)	Progressor ($n=516$)	*P*-value
Sex			0.231
Male (%)	415 (48.6%)	273 (52.9%)	
Female (%)	438 (51.3%)	243 (47.1%)	
Age (SD)	79.55 (8.08)	80.46 (8.24)	0.046
Education (SD)	7.14 (5.09)	7.30 (5.22)	0.572
BMI (SD)	23.49 (3.90)	22.91 (4.20)	0.010
Living			0.329
Alone (%)	18 (2.8%)	12 (3.1%)	
Home (%)	515 (79.4%)	291 (75.4%)	
Institution (%)	116 (17.9%)	83 (21.5%)	
Cognition assessment			
MMSE (SD)	14.26 (6.07)	14.61 (6.09)	0.294
CDR	1.14 (0.53)	1.18 (0.53)	0.173
CDR box	6.60 (3.38)	7.13 (3.27)	0.005
CASI	52.44 (18.60)	51.08 (18.96)	0.191
Physical comorbidities			
SAE (%)	596 (77.7%)	380 (81.0%)	0.165
Diabetes mellitus (%)	167 (19.6%)	109 (21.1%)	0.483
Arterial hypertension (%)	304 (35.6%)	196 (38.0%)	0.382
Coronary artery disease (%)	342 (40.0%)	189 (36.7%)	0.218
Dyslipidemia (%)	207 (24.2%)	117 (22.7%)	0.509
Chronic kidney disease (%)	290 (34.0%)	149 (28.9%)	0.054
Anemia (%)	89 (10.4%)	45 (8.7%)	0.303
Abnormal liver enzyme (%)	196 (23.0%)	100 (19.4%)	0.120
Hyper-T4 (%)	32 (3.7%)	17 (3.3%)	0.662
Hypo-T4 (%)	2 (0.2%)	1 (0.2%)	0.877
Hypo-vitamin B12 (%)	9 (1.1%)	10 (1.9%)	0.175
Hypo-folate (%)	52 (6.1%)	39 (7.6%)	0.290
Nonphysical comorbidities			
Depression	76 (8.9%)	52 (10.1%)	0.468
BZRA (%)	212 (24.8%)	164 (31.8%)	0.005
Antidepressant (%)	108 (12.6%)	69 (13.4%)	0.698
Antipsychotics (%)	141 (16.5%)	130 (25.2%)	**<0.001**
Medication: AChEIs			0.014
Donepezil	628 (73.5%)	353 (68.4%)	
Rivastigmine	158 (18.5%)	129 (25.0%)	
Galantamine	68 (8.0%)	34 (6.6%)	

Note: Bold type indicated statistical significance.

Abbreviations: AChEIs, acetylcholinesterase inhibitor; BMI, body mass index; BZRA, benzodiazepine receptor agonist; CASI, Cognitive Abilities Screening Instrument; CDR, Clinical Dementia Rating scale; MMSE, mini-mental state examination; SAE, subcortical arteriosclerotic encephalopathy; SD, standard deviation; T4, free thyroxine.

decline after 1 year of AChEI treatment. The relationship between BMI and AD is bidirectional. Previous studies have found that a higher BMI in midlife was related to a higher risk of developing dementia, but a higher BMI in late life seems to be cognitively protective, with a reduced risk of developing subsequent dementia.[22] Consistent with our findings, several studies have demonstrated that maintaining body weight in late life is protective for cognitive function, while unintentional weight loss and reduced lean mass contribute to cognitive decline.[23] There is a triad of interactions among frailty, sarcopenia, and immunosenescence that explain the detrimental effect of unintentional weight loss in late life on cognitive function.[24] Unintentional weight loss, caused by chronic diseases and medication side effects, results in the loss of lean mass, frailty, and sarcopenia. Similarly, malnutrition secondary to unintentional weight loss may cause immune system dysfunction. Malnutrition may impair innate and adaptive pathways through an impaired epithelial barrier in the skin and gut, with fewer circulating dendritic cells, reduced B cells, soluble IgA, and atrophic lymphoid organs.[25] Studies have also suggested that immunosenescence may contribute to cognitive decline due to central nervous system damage and chronic systemic inflammation.[26] More recently, a systemic review published in 2023 suggest that adequate supplement of nutrition with diet consist of unsaturated fatty acid and vitamin is benefit for AD patient. It may reduce the oxidative stress and inflammation effect, therefore delay the cognitive function decline.[27] In summary, the avoidance of unintentional weight loss and maintenance of BMI could prevent frailty, sarcopenia, and the immunosenescence triad in patients with AD, which may explain the negative impact of lower BMI in patients with AD receiving AChEIs.

Another finding of the present study was that patients with AD who were concurrently treated with antipsychotic agents were more likely to experience cognitive decline, which is consistent with the findings of previous studies.[28] An observational study including 8034 patients with AD found that the usage of antipsychotics was associated with a greater decline in the MMSE over a 2-year period compared to exposure to other psychotropic agents.[29] The use of antipsychotics might result from the intention to treat BPSD in patients with AD, who suffer from a more complicated and severe clinical course.[29] BPSD is characterized by behavioral, perceptual, mood, and thought disturbances in up to 90% of patients with dementia during the disease course.[30] BPSD is associated with a greater caregiver burden, worse quality of life, and increased mortality.[31] In addition to these symptoms, the presentation of psychosis and affective symptoms in BPSD also predicts accelerated cognitive decline in patients with dementia.[32] Pharmacological treatments include antipsychotics, with approximately 20%–50% of patients with BPSD being prescribed antipsychotics.[33] However, there is limited evidence on the use of antipsychotics in the treatment of BPSD, and they may also have a detrimental effect on the disease progression of dementia.[34] An RCT including 421 patients with AD found a significant decline in most cognitive areas, with a progression of 2.4 points in the MMSE over 36 weeks compared to controls, when participants routinely used antipsychotics, especially olanzapine and risperidone.[34]

TABLE 2 Comparison of cognition assessment outcomes between progressors and nonprogressors.

	Difference between the 1st & 2nd assessments (1st–2nd)			Difference of CASI value progression between nonprogressors and progressors	
	Nonprogressor ($n = 854$)	Progressor ($n = 516$)	*p*-value	Mean	95%CI
MMSE	−1.110 (2.699)	5.060 (3.252)	<0.001	−6.172	−6.509 to −5.836
CDR	−0.020 (0.184)	−0.448 (0.546)	<0.001	0.428	0.379 to 0.477
CDR-box	−0.726 (1.653)	−2.957 (2.529)	<0.001	2.231	1.984 to 2.478
CASI(SD)	−1.224 (8.953)	13.574 (10.704)	<0.001	−14.798	−15.906 to −13.690
LTM	0.093 (1.932)	1.288 (2.502)	<0.001	−1.196	−1.449 to −0.943
STM	−0.235 (2.603)	1.228 (2.224)	<0.001	−1.464	−1.735 to −1.193
ATTEN	−0.330 (1.939)	1.370 (2.169)	<0.001	−1.699	−1.928 to −1.470
MENMA	−0.260 (2.127)	1.510 (2.427)	<0.001	−1.773	−2.027 to −1.518
ORIENT	−0.050 (3.237)	3.040 (3.369)	<0.001	−3.091	−3.455 to −2.727
ABSTR	0.024 (2.047)	1.316 (2.249)	<0.001	−1.293	−1.532 to −1.054
LANG	−0.272 (1.529)	1.309 (1.864)	<0.001	−1.582	−1.774 to −1.390
DRAW	−0.088 (2.595)	1.425 (2.902)	<0.001	−1.512	−1.819 to −1.205
ANML	−0.070 (2.116)	0.990 (2.098)	<0.001	−1.066	−1.297 to −0.835

Abbreviations: ABSTR, abstract thinking; ANML, word fluency (Animal); ATTEN, attention; CASI, cognitive abilities screening instrument; CDR, Clinical Dementia Rating scale; CI, confidence interval; DRAW, drawing; LANG, Language; LTM, long-term memory; MENMA, mental manipulation; MMSE, mini-mental state examination; ORIENT, orientation; SD, standard deviation; STM, short-term memory.

TABLE 3 Logistic regression of predisposing factors for incident progression after acetylcholinesterase inhibitor prescription.

Covariables	Adjust-OR	S.E.	*B*	*p*	95% CI
Age	1.011	0.007	0.011	0.147	0.996–1.025
Female	1.162	0.118	1.114	0.202	0.922–1.465
BMI	**0.970**	0.024	−0.031	**0.033**	0.943–0.997
Antipsychotics	**1.599**	0.146	0.452	**0.001**	1.202–2.128
BZRA	1.290	0.142	0.255	0.054	0.996–1.672
Donepezil	1.093	0.234	0.069	0.691	0.705–1.695
Rivastigmine	1.548	0.245	0.437	0.075	0.958–2.503
Galantamine	Reference				

Note: Bold type indicates statistical significance.

Abbreviations: BMI, body mass index; BZRA, benzodiazepine receptor agonist; CDR, Clinical Dementia Rating scale; CI, confidence interval; OR, odds ratio; SE, standard error.

Among the many adverse effects of antipsychotic use, the increased risk of cardiovascular events was most closely related to the deterioration of cognitive function in patients with dementia. A meta-analysis that included 16 RCTs and 3343 participants found a double risk (OR 2.5) of cardiovascular events when investigating the safety of atypical antipsychotic treatments in patients with dementia.[35] Cardiovascular events associated with antipsychotic use cause brain damage, thus precipitating neurodegenerative disorders in patients with AD.[36] Furthermore, experts exploring the mechanism of association between BPSD and progression of AD disease course illustrate a neurochemical changes model. They have found evidence including the pathophysiological cholinergic-dopaminergic system dysregulation.[18] The monoaminergic alteration co-occur with cholinergic system changes are observed in the experimental model in recent years.[37] The usage of antipsychotic may predispose the dysregulation of the system and bring up more disease symptoms. Overall, the risk of cognitive decline due to antipsychotics prescribed to patients with AD warrants further investigation so that safer pharmacological treatments for BPSD can be identified.

Third, we found that the concurrent use of BZRA was associated with a significant negative trend. In the present study, more than a quarter of the patients had concurrent BZRA use in the first year of diagnosis. The percentage of usage was similar to previous studies, which reported that between 15% and 30% of elderly patients are prescribed BZRA.[38] Our findings also support several previous studies that recommended avoiding the use of BZRA in patients with AD.[39,40] BZRA are associated with significant adverse side effects in elderly individuals, including drowsiness, lethargy, impaired motor coordination, dizziness, vertigo, hostility, and erratic behavior. Furthermore, patients with dementia are more vulnerable to the adverse effects of BZRA and have increased risks of morbidity and care burden.[40] Past review studies suggested that the combined use

of BZRA in patients with dementia may impair cognitive function.[39] Hessmann et al. conducted a cross-sectional study that compared BZRA users and nonusers among 395 patients with AD. Lower self-care function and higher mood disturbances were found in BZRA users among the patients with AD.[41] In general, the combined use of BZRA in patients with AD appears to interfere with the treatment effect of AChEIs.

Our study illustrate some factors that have associated with treatment effect of AChEIs in Asia's AD patients in both outpatient and inpatient settings. The clinicians may found benefit by maintaining the BMI to avoid unintentional body weight loss, which are often associate with side effect of anorexia.[42] They also need to be cautious and avoiding the prescription of antipsychotic and BZRA. When the medication are used under necessary condition, the clinicians need to shorten the prescription duration and put effort in preventing the possible side effect. By doing so, the cognitive function decline may be slow down under the treatment of AchEIs.In our study we reviewed more than a thousand patient's detailed demographic data, medical records and cognitive function evaluation. One of the strength of our study is that the group of the patient we included in our study represent general elderly population in Asian. Although we only include patient from one medical center, the participant are not only hospitalized patient but also those who lived at home or lived in nursing home. Another strength is that the patient came to our hospital are mainly veterans, and they tempted to follow-up in our hospital's both outpatient and inpatient services with high adherence. Such characteristic guarantee the detailed and longitudinal information of their medical records with high validity. In addition, current study with observational design indicate that our findings are closer to the real world treatment condition. To sum up, our findings may offer clinicians with more consideration when treating AD patient with AChEIs in both outpatient and inpatient settings.

4.1 | Limitations

This study has several limitations. First, the data were derived from a single medical center over a 1-year follow-up period, and the findings may not be generalizable to other populations, settings, or longer follow-up periods. Second, we could only assess the medical records at our hospital. Several potential confounding factors, such as a family history of dementia, quality of care, lifestyle, daily diet, the patient's past history that was beyond recognition such as substance abuse, and numerous medication that would affect the cognitive function, were not considered in this study. In addition, the medication exposure is defined based on the medical record, which only include the prescription in our hospital. However, the patients include in our study are majorly veterans and their spouse, which probably indicate a inclusively medical visit in our hospital that guarantee the generalizable of medical record. Third, given the nature of the study design, the causal effects that impact the treatment effectiveness of AChEIs on cognition could not be determined. Forth, we did not include the measurement for the severity of neuropsychiatric symptoms. The measurement for the severity of neuropsychiatric symptoms was not a regular performance in clinical environments in our hospital. The covariate of neuropsychiatric symptom between the antipsychotic usage and cognitive outcome may need further evaluations. Fifth, the diagnosis of AD in our participants lacked more precise medical examination such as analysis of Cerebrospinal Fluid (CSF) or Amyloid-image Positron Emission Tomography (PET). This is because that those examination are seldom performed in Taiwan's clinical environment in consideration of their intrusiveness and expensiveness. We made efforts to improve the specificity of our diagnosis by reviewing the medical records of the participants repetitively, and exclude them from the studies once the AD diagnosis was revised by their doctors.

5 | CONCLUSION

In the present 1 year follow-up retrospective cohort study, we found that a lower baseline BMI and antipsychotics were risk factors for cognitive function decline in patients with AD receiving AChEI treatment. Furthermore, the prescription of BZRA in patients with AD may deteriorate cognitive function. Clinicians should carefully assess the benefits and disadvantages of prescribing these medications to patients with AD.

AUTHOR CONTRIBUTIONS

C.S.C. designed the study and wrote the protocol. T.W.H. and P.Y.C. drafted the manuscript. C.H.C. and C.C.P. analyzed the data. C.H.C., Y.C.C., C.C.P., H.Y.K., and assisted with the preparation and proofreading of the manuscript. T.W.H provided the advice on statistical analysis. C.S.C. supervised this program. All authors agreed the submission and publication of this paper.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest has been reported by the authors.

ETHICAL APPROVAL

The study protocol was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (21-CT4-05). The requirement for informed consent was waived according to the regulations of our IRB.

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