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Polypharmacy and cognitive outcomes in elderly inpatients with Alzheimer's disease: A three-year retrospective study

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Abstract: **Background**: Inpatient care for Alzheimer's disease (AD), often complicated by comorbidities, frequently involves polypharmacy (≥5 medications). The profile and cognitive consequences of sustained polypharmacy in these elderly inpatients require further investigation. **Objectives**: To investigate the status of polypharmacy in elderly inpatients with AD and its correlation with three-year cognitive outcomes, so as to provide a basis for clinical optimization of medication regimens. **Methods**: This study was a retrospective propensity score matching (PSM) cohort study. 300 AD inpatients who were hospitalized from March 2022 to March 2025 were included. Patients were stratified into polypharmacy and non-polypharmacy groups according to their polypharmacy status. The primary outcome was the incidence of cognitive decline (MMSE decline ≥3 points) at 3 years. Secondary outcomes were the association of CDR progression, rate of decline in MoCA, incidence of falls, all-cause rehospitalization, all-cause mortality and anticholinergic drug burden with cognitive outcomes. **Results**: After PSM, baseline characteristics were balanced (p>0.05). At the 3-year follow-up, the polypharmacy group had a significantly higher incidence of cognitive decline than the non-polypharmacy group (64.0% vs. 38.0%; RR=1.68, 95% CI: 1.33-2.13, p<0.001). Polypharmacy was also associated with faster CDR progression, a greater annual rate of MoCA decline and increased risks of falls (RR=1.82, p<0.01) and all-cause rehospitalization (RR=1.67, p<0.001). A high anticholinergic burden (ACB score ≥3) was identified as an independent predictor of cognitive decline (OR=2.5, 95%CI: 1.7-3.7, p<0.001). **Conclusions**: Our findings highlight polypharmacy as a key, modifiable risk for cognitive decline in AD, calling for structured medication management to mitigate this risk.

Keywords: Alzheimer's disease; Cognitive decline; Incidence rate; Polypharmacy; Propensity score matching; Risk factors

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INTRODUCTION

Alzheimer's disease (AD) is the predominant neurodegenerative condition in the aging population. Defined by its progressive nature, the cognitive and behavioral impairment in AD presents an escalating public health burden worldwide (Su *et al.*, 2024). With the deepening of global aging, the prevalence of AD is increasing year by year. AD affects approximately 3.2% of the population over 65, with a notably higher risk in the 75-80 age bracket(GBD 2019 Dementia Forecasting Collaborators, 2022). The clinical characteristics of such patients are distinct. AD not only diminishes self-care ability and quality of life through cognitive decline but also, due to common comorbidities like hypertension and diabetes, makes complex polypharmacy regimens particularly prevalent(Sepulveda Gallardo *et al.*, 2025; Amanda *et al.*, 2025).

Characterized by the sustained use of ≥5 drugs, polypharmacy is highly prevalent among older adults, affecting up to 70.8% of this population (Tian *et al.*, 2022). Owing to a higher comorbidity burden and intricate management needs, individuals with AD face a heightened risk of polypharmacy versus their cognitively healthy peers (Al-Azayzih *et al.*, 2024; Frahm *et al.*, 2021). In clinical practice, the medication regimen of AD patients often includes symptomatic treatments such as cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists, as well as medications for chronic conditions (e.g., antihypertensives, hypoglycemics) and preventive drugs (e.g., antiplatelet agents, vitamin supplements). Some patients even take more than 10 drugs at the same time, forming a state of excessive polypharmacy (Gareri *et al.*, 2024; Hung *et al.*, 2025). While polypharmacy meets the treatment needs of a variety of diseases, it also brings a series of clinical problems: the interaction between drugs may reduce the therapeutic effect and increase the risk of adverse reactions, which is further amplified by the physiological decline of liver and kidney function and the decline of drug metabolism in elderly AD patients (Otani *et al.*, 2024).

Maintenance of cognitive function is one of the core goals of the clinical management of AD patients, and the association between polypharmacy and cognitive outcomes has become a research hotspot in geriatrics and neurology in recent years. As early as 1988, reported 3 elderly patients with acute confusion caused by multiple drugs and their physical and mental conditions were significantly improved after adjusting the drug regimen. Elderly patients are more susceptible to AD, especially for AD patients with existing cognitive impairment; irrational

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drug use may accelerate cognitive decline(Reallon *et al.*, 2024). However, there are still many shortcomings in current related studies. Most of these studies are cross-sectional designs or short-term follow-up and lack long-term (≥3 years) longitudinal data for AD patients. This complexity obscures the causal relationship between polypharmacy and cognitive progression Research populations have mostly focused on community-dwelling AD patients. In contrast, hospitalized AD patients are usually more severe, with more complex comorbidities and more medications. The characteristics of polypharmacy and its impact on cognitive outcomes remain poorly understood. In terms of research methods, some studies did not fully control for confounding factors such as age, number of comorbidities and baseline cognitive function, thereby compromising the validity of the results. There is a high proportion of patients with low education level in AD and the sensitivity of cognitive assessment and medication compliance in this population are special. Studies on polypharmacy in this subgroup are more scarce.

Given the above gaps in clinical research, this study adopted a retrospective propensity score-matching (PSM) cohort design to include hospitalized elderly AD patients and balance baseline confounding factors between the two groups. The associations between polypharmacy and 3-year cognitive outcomes (including the incidence of cognitive decline and clinical dementia rating (CDR) progression) and other clinical outcomes (falls, rehospitalization, death) were systematically analyzed, and the impact of anticholinergic drug burden on cognitive outcomes was explored. The following hypothesis is proposed that polypharmacy elevates the risk of 3-year cognitive decline (reflected by CDR progression and rapid montreal cognitive assessment (MoCA) decrease), falls and rehospitalization in elderly AD inpatients, but not mortality. An anticholinergic cognitive burden (ACB) score ≥3 was hypothesized to compound this cognitive risk. The findings are intended to support the implementation of structured medication reviews and deprescribing for better long-term prognosis.

Significance & Innovation: Using propensity score matching, this study investigated the association between polypharmacy and long-term cognitive/safety outcomes in elderly AD inpatients. Results identified polypharmacy as an independent risk factor for cognitive decline, offering an evidence base for optimizing medication regimens.

MATERIALS AND METHODS

Study design

This study was a retrospective PSM cohort study. AD patients hospitalized from March 2022 to March 2025 were included. According to the Chinese Expert Consensus on the Evaluation and Management of Polypharmacy for the Elderly (Shen *et al.*, 2024), polypharmacy was defined as the use of ≥5 drugs at the same time and patients were stratified into polypharmacy (n=164) and non-polypharmacy (n=166) groups from medical records. Following 1:1 propensity score matching for confounders (e.g., age, baseline mini-mental state examination (MMSE)), 150 matched pairs were generated for analysis (Fig. 1).

Inclusion and exclusion criteria

Inclusion criteria: A diagnosis of Alzheimer's disease was based on the core criteria established by the National Institute of Neurology, Language Disorders and Stroke Institution-AD and Related Disorders Association (NINCDS-ADRDA)(Jack *et al.*, 2024), The diagnosis was confirmed by clinical symptoms, neuropsychological evaluation, head CT/MRI and laboratory examination (reversible cognitive impairment factors such as thyroid dysfunction and vitamin B12 deficiency were excluded); age ≥65 years old; Hospital stay ≥24 hours, complete 3-year follow-up and complete clinical data (medical records, doctor's orders, medication lists, examination reports and laboratory/imaging examination reports.); The education level was mainly primary school and the neuropsychological assessment could be completed in the medical record or reliable clinical information could be provided by family members.

Exclusion criteria: Other forms of dementia (e.g., vascular dementia or dementia with Lewy bodies), or whose records indicated a cognitive impairment inconsistent with a pure AD diagnosis; patients with severe mental illness (e.g., schizophrenia, major depressive episode); the baseline MMSE score was less than 10 points (according to the first neuropsychological assessment record at admission, the severe cognitive function impairment resulted in limited reference value of subsequent assessment data) (Davis *et al.*, 2021); the expected survival time of patients with end-stage diseases (such as advanced cancer, New York Heart Association (NYHA) class IV) <3 years; patients with serious missing baseline data or lost to follow-up.

Observation indicators

Study data were retrospectively collected from institutional electronic health records, laboratory databases and nursing documentation systems.

Baseline data

Collected baseline data encompassed demographics, anthropometrics, and comorbidity profiles, including conditions such as hypertension and diabetes; baseline neuropsychological assessment results (MMSE, CDR, MoCA scores); type and number of medications; and ACB score. The relevant data were extracted from hospitalization medical records, laboratory test reports and, and nursing records.

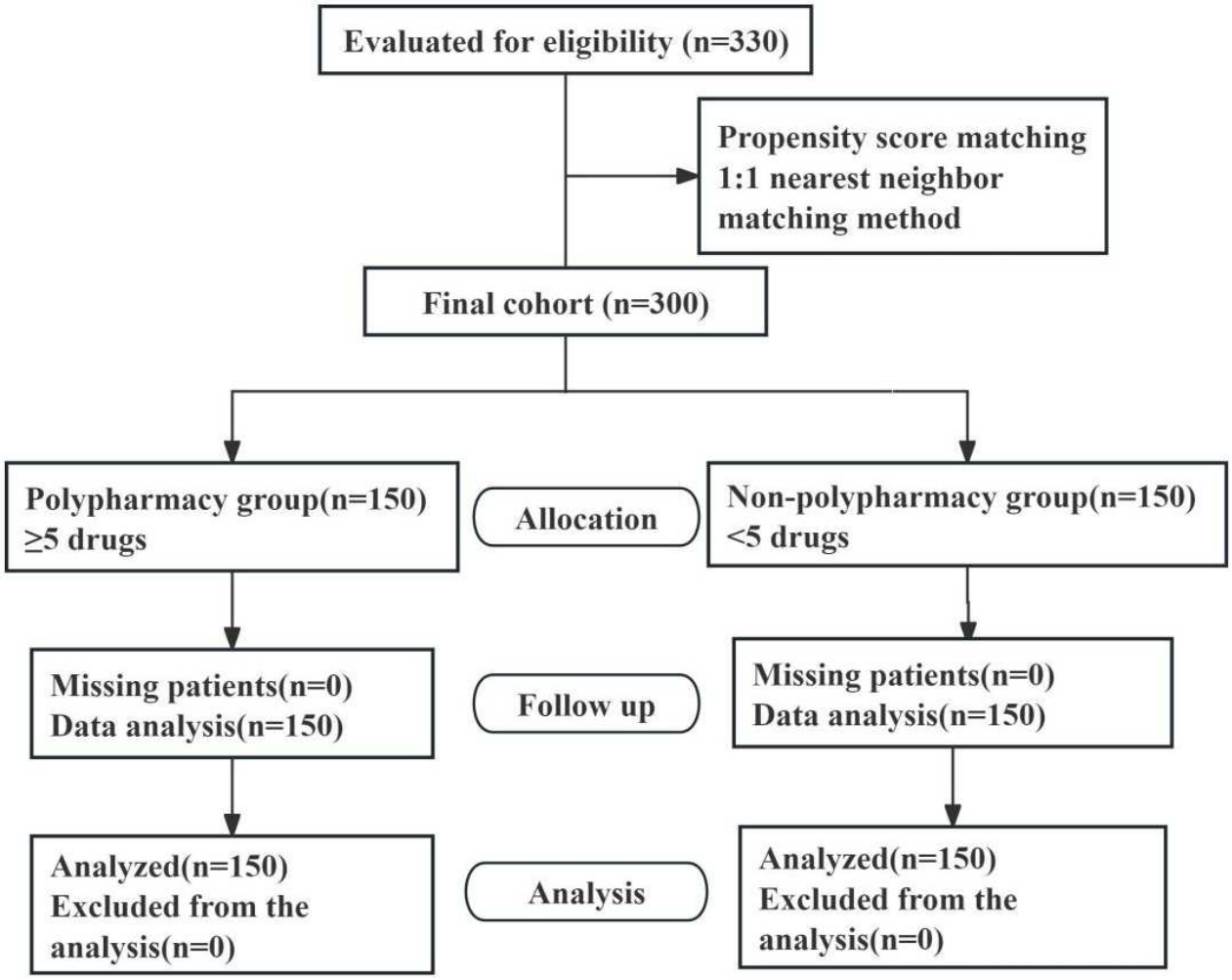

Fig. 1: Flow chart of the study

Main outcome measures

Incidence of significant cognitive decline during the 3-year follow-up: Defined as a decline of ≥3 points from baseline on the MMSE (Quinn et al., 2021). Score results were obtained from complete neuropsychological assessment records during the follow-up period.

Secondary outcome measures

Progression of clinical dementia rating: Defined as the proportion of patients whose CDR score progressed from baseline ≤ 1 to ≥ 2 and the score results were obtained from the neuropsychological assessment report recorded in the medical record (Peakman *et al.*, 2022).

MoCA decline rate: Based on baseline and follow-up MoCA score records, the total decline was calculated and converted to an average annual decline (Caminiti *et al.*, 2025).

Safety outcomes: The outpatient medical records, emergency department records, family feedback records, and telephone follow-up registration during the follow-up period were reviewed to calculate the number and proportion of patients who fell for any reason (including minor falls without injury, soft tissue injury or fracture caused by falls) and the frequency of all-cause hospitalization during the 3-year follow-up.

Survival outcome: The number and proportion of patients who died of any cause within 3 years of follow-up were counted from family follow-up records, death certificates, and household registration information.

Drug-specific analysis: The association between anticholinergic drug burden and cognitive outcomes was evaluated, and the ACB scale was used to score based on patients' medication records (Joshi *et al.*, 2021).

Sample size calculation

An independent-samples t-test in G*Power 3.1 was used to calculate sample size, based on the anticipated incidence of cognitive decline. Referring to previous similar studies that polypharmacy was a significant risk factor for cognitive impairment (risk ratio (RR)=1.39) (Yu *et al.*, 2024),

combined with the preliminary statistics of clinical follow-up data of AD patients in our hospital, the calculation presumed cognitive decline rates of 38% (non-polypharmacy) and 64% (polypharmacy). The RR of 1.39 was converted to a Cohen's h effect size of approximately 0.4, representing a medium effect, for input into G*Power, with α set at 0.05 (two-sided) and power at 80%. Preliminary calculations showed that a minimum of 131 patients per group would be required. To ensure that the final sample size included in the analysis was adequate and to fully account for the possible sample loss during PSM, as well as the 10% cases of incomplete data or dropout in retrospective studies, the sample size was expanded to 150 cases in each group, and the final total sample size was 300 cases.

Statistical analysis

All analyses used SPSS 26.0, using two-tailed tests with a $p<0.05$ threshold. Continuous measures were reported as mean ± SD or median and compared using parametric or non-parametric tests depending on their distribution. Categorical measures were summarized as frequencies (%) and compared via chi-square or Fisher's exact tests. To reduce confounding by baseline characteristics between groups, PSM was used to balance. A logistic regression model was constructed to estimate a propensity score for each patient, selecting variables that might affect polypharmacy and cognitive outcomes. The matching covariates were age, sex, BMI, education, baseline MMSE, comorbidity count and histories of hypertension, diabetes and coronary heart disease. A 1:1 nearest-neighbor matching with a caliper of 0.02 was then applied. After matching, a balanced cohort of 150 patients per group was formed for subsequent analysis. The primary and selected secondary outcomes (CDR progression rate, falls, rehospitalization, mortality) were expressed as hazard ratios with 95% confidence interval (CI) and tested using chi-square tests. Continuous variables, such as annual decline in MoCA scores, were compared using t-tests. To identify independent risk factors for cognitive decline, variables that showed a potential association in univariate analyses (using a liberal threshold of $p<0.1$ for screening purposes) and those with clear clinical significance were included in the multivariate Logistic regression model to calculate odds ratio (OR) and their 95% CI. In this final multivariate model, statistical significance was defined as $p<0.05$ (two-tailed). The model specifically included anticholinergic drug burden as a key independent variable.

RESULTS

Comparison of baseline data

The initial cohort comprised 330 AD inpatients, with 164 and 166 assigned to the polypharmacy and non-polypharmacy groups, respectively. The patient selection process is detailed in fig. 1. To control for potential confounding bias, PSM was used to perform 1:1 matching, and 300 inpatients were successfully matched: 150 in the polypharmacy group and 150 in the non-polypharmacy group (Table 1). Before matching, the polypharmacy and non-polypharmacy groups showed significant imbalances ($p<0.05$), including older age, lower MMSE/MoCA scores and a higher proportion of CDR=2 in the polypharmacy group. The polypharmacy group also carried a significantly greater comorbidity burden, both in the number of conditions and the prevalence of specific diseases, notably hypertension and diabetes. These differences are in line with the clinical reality that patients with more comorbidities and severe illness are more likely to suffer from polypharmacy. Still, they also highlight the serious bias of directly comparing the outcomes of the two groups and confirm the need for PSM. After matching, the groups demonstrated comparability across all measured demographic data (age, gender, education level) and clinical indicators (body mass index, MMSE score, MoCA score, baseline CDR stage), with no significant differences observed (all $p>0.05$). The only difference expected and allowed was the number of medications used ($p<0.001$), as this was the exposure in the study. The results showed that PSM successfully balanced known potential confounders between the polypharmacy and non-polypharmacy groups, resulting in a cohort with highly comparable baseline characteristics.

Comparison of incidence of cognitive decline

As summarized in table 2, the polypharmacy group demonstrated a consistently elevated risk of cognitive decline over the 3-year follow-up. By year three, the cumulative incidence reached 64.0% (96/150), markedly exceeding the 38.0% (57/150) in controls (RR=1.68, $p<0.001$). This analysis confirms polypharmacy as an independent risk factor for long-term cognitive decline in elderly AD inpatients after adjusting for confounders.

Comparison of CDR progression rates

This analysis was restricted to the baseline mild dementia (CDR≤1) subcohort, with 119 and 122 patients in the polypharmacy and non-polypharmacy groups, respectively.

As presented in table 3, the polypharmacy group demonstrated a significantly greater progression rate to moderate or severe dementia (CDR ≥2) over 3 years compared with the non-polypharmacy group (35.3%(42/119) vs. 15.6%(19/122)). The hazard ratio for polypharmacy leading to CDR progression was as high as 2.27 (95% CI: 1.39-3.70), and the risk difference was highly statistically significant ($p=0.001$), indicating that polypharmacy was a strong predictor of advancing the overall disease stage of AD.

Comparison of annual rate of decline of MoCA

Comparable baseline MoCA scores ensured initial group parity. As shown in table 4, the polypharmacy group subsequently exhibited lower scores at all follow-up assessments, with this cognitive gap diverging progressively over time.

Table 1: Comparison of baseline characteristics between polypharmacy and non-polypharmacy groups before and after propensity score matching

Indicators	Before PSM				After PSM			
	Polypharmacy group (n=164)	Non-Polypharmacy group (n=166)	statistic	*p*-value	Polypharmacy group (n=150)	Non-Polypharmacy group (n=150)	statistic	*p*-value
Demographics								
Age (years)	77.8 ± 5.2	76.1 ± 5.8	t=2.829	0.005	77.3 ± 5.1	77.2 ± 5.2	t=0.167	0.867
Sex (Male/Female)	78/86	85/81	χ^2=0.430	0.512	73/77	72/78	χ^2=0.055	0.815
Body Mass Index (kg/m²)	23.1 ± 2.5	23.5 ± 2.7	t=1.401	0.162	23.4 ± 2.5	23.4 ± 2.6	t=-0.198	0.843
Education level [n(%)]			χ^2=8.102	0.017			χ^2=0.145	0.93
- *Primary school*	148 (90.2%)	152 (91.6%)			142 (94.7%)	140 (93.3%)		
- *Junior high or above*	16 (9.8%)	14 (8.4%)			8 (5.3%)	10 (6.7%)		
Clinical characteristics								
MMSE score	19.5 ± 3.1	20.3 ± 3.4	t=2.329	0.021	19.6 ± 3.1	20.2 ± 3.1	t=-1.788	0.075
MoCA score	16.2 ± 2.8	16.9 ± 3.0	t=2.172	0.031	16.4 ± 2.7	16.6 ± 3.0	t=-0.787	0.432
Baseline CDR Stage [n(%)]			χ^2=11.789	0.003			χ^2=0.186	0.912
- *CDR 0.5 (Questionable)*	25 (15.2%)	40 (24.1%)			24 (16.0%)	25 (16.7%)		
- *CDR 1 (Mild)*	98 (59.8%)	108 (65.1%)			95 (63.3%)	97 (64.7%)		
- *CDR 2 (Moderate)*	41 (25.0%)	18 (10.8%)			31 (20.7%)	28 (18.6%)		
Number of comorbidities	4.8 ± 1.2	3.5 ± 1.1	t=11.146	<0.001	4.6 ± 1.2	4.5 ± 1.1	t=0.570	0.569
Comorbidities [n(%)]								
- *Hypertension*	132 (80.5%)	115 (69.3%)	χ^2=5.899	0.015	118 (78.7%)	115 (76.7%)	χ^2=0.169	0.682
- *Diabetes Mellitus*	75 (45.7%)	58 (34.9%)	χ^2=4.096	0.043	65 (43.3%)	62 (41.3%)	χ^2=0.124	0.724
- *Coronary Heart Disease*	68 (41.5%)	55 (33.1%)	χ^2=2.623	0.105	60 (40.0%)	58 (38.7%)	χ^2=0.056	0.813
- Hyperlipidemia	89 (54.3%)	82 (49.4%)	χ^2=0.808	0.368	80 (53.3%)	78 (52.0%)	χ^2=0.055	0.815
Medication-related indicators								
Number of Medications	6.5 ± 1.1	3.2 ± 0.9	t=31.421	<0.001	6.4 ± 1.1	3.4 ± 0.9	t=25.578	<0.001
ACB Score ≥ 3 [n(%)]	75 (45.7%)	45 (27.1%)	χ^2=13.202	<0.001	62 (41.3%)	58 (38.7%)	χ^2=0.230	0.631

Note: PSM: Propensity Score Matching; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; ACB: Anticholinergic Cognitive Burden.

Table 2: Cumulative incidence of significant cognitive decline (MMSE Reduction ≥3 Points) in both groups over the 3-year follow-up period [n(%)]

Group	n	Cognitive decline at year 1	Cognitive decline at year 2	Cognitive decline at year 3	Risk ratio (RR)	95% Confidence interval	χ^2 Value	*p* Value
Polypharmacy group	150	25 (16.7%)	63 (42.0%)	96 (64.0%)	1.68	1.33-2.13	18.72	<0.001
Non-Polypharmacy group	150	10 (6.7%)	32 (21.3%)	57 (38.0%)				

The MoCA score of polypharmacy decreased from 16.4 at baseline to 11.2 at the third year, with a cumulative decline of 5.2 points and an average annual rate of decline of 1.7 ± 0.6 points. In the non-polypharmacy group, the decline was more gradual, from 16.6 to 13.5, with a cumulative decline of 3.1 points and an average annual decline rate of 1.0 ± 0.7 points. The intergroup difference in the mean annual decline rate was highly statistically significant (p<0.001). This finding indicates that polypharmacy not only independently predicts cognitive impairment but also markedly accelerates its progression in AD patients.

Safety outcome analysis

The comparative analysis of safety outcomes between the two cohorts is summarized in table 5. Over the three-year follow-up period, falls occurred in 22.0% (33/150) of participants in the polypharmacy group, a rate significantly greater than the 12.0% (18/150) observed in the non-polypharmacy group. The relative risk of falling was 1.82 times higher among those receiving multiple medications (RR=1.82, 95% CI: 1.07–3.11, p=0.002). Similarly, regarding healthcare utilization, the all-cause rehospitalization rate reached 50.0% (75/150) in the polypharmacy group, markedly exceeding the 30.0% (45/150) recorded in the non-polypharmacy group. This corresponds to a 1.67-fold increase in rehospitalization risk for the polypharmacy cohort (RR=1.67, 95% CI: 1.25-2.22, p<0.001). These findings strongly indicate that polypharmacy constitutes a significant risk factor for both falls and elevated healthcare burden in older adults with AD.

Survival outcome analysis

Regarding long-term survival, the 3-year follow-up data revealed 22 fatalities (14.7%) in the polypharmacy cohort, compared with 19 (12.7%) in the non-polypharmacy group. As summarized in table 6, although the polypharmacy group exhibited a 16% elevation in mortality risk relative to the non-polypharmacy group, this difference in all-cause mortality was not statistically significant (RR=1.16, 95% CI: 0.80–1.68, p=0.42).

Association analysis between anticholinergic drug burden and cognitive decline

To determine the independent effect of the burden of specific medications in polypharmacy on cognitive outcomes, multivariate Logistic regression analyses were performed. As shown in table 7, multivariable analysis, adjusted for age, sex, baseline MMSE and comorbidity count, identified a high anticholinergic burden (ACB score≥3) as an independent predictor of significant cognitive decline (defined as an MMSE reduction of ≥3 points) at the 3-year follow-up (OR=2.5, 95% CI: 1.7-3.7, p<0.001).

DISCUSSION

In this three-year retrospective propensity-matched cohort study, polypharmacy was independently associated with adverse long-term cognitive outcomes in hospitalized Alzheimer's disease patients. After accounting for baseline confounding variables, polypharmacy was associated with a 68% heightened risk for substantial cognitive decline (RR=1.68). Additionally, exposure to multiple medications correlated with both accelerated disease severity progression and an increased velocity of overall cognitive impairment. With respect to safety outcomes, polypharmacy significantly increased risks for falls and all-cause rehospitalization. Multivariate regression analysis further revealed that higher anticholinergic drug burden (ACB≥3) was a strong independent predictor of cognitive decline (OR=2.5). These findings provide an important evidence-based basis for medication management in elderly inpatients with AD.

These findings align with earlier research in this area. A meta-analysis of 27 studies demonstrated that the concurrent use of five or more medications was significantly associated with an increased risk of cognitive impairment in older adults (OR=1.39, 95% CI: 1.23–1.58) (Yu *et al.*, 2024). Furthermore, a one-year multicenter cohort study reported that approximately 50% of older adults with mild cognitive impairment (MCI) used more than three medications daily. After one year of follow-up, the polypharmacy group exhibited a sixfold higher risk of progressing to dementia compared to those taking fewer than three medications (Trevisan *et al.*, 2021). The reasons for this are the physiological decline of liver and kidney function in elderly AD patients, the decreased ability of drug metabolism and clearance, the accumulation of drugs easily caused by polypharmacy and the interaction between different drugs may affect the absorption and efficacy of core therapeutic drugs for AD (such as cholinesterase inhibitors) (Muñoz-Contreras *et al.*, 2024; Ngcobo, 2025). In addition, the comorbidities of hospitalized AD patients are more complex and the types of drugs are mostly involved in cardiovascular, metabolic and other systems.

The adverse reactions of central nervous system (such as drowsiness and distractness) of some drugs may directly aggravate cognitive impairment, especially for patients with low education level, whose cognitive reserve is low and their tolerance to adverse drug effects is worse (Ma *et al.*, 2020). This study further revealed that polypharmacy is not merely associated with cognitive impairment but appears to accelerate its progression. The sensitivity of MoCA scale to mild cognitive impairment is higher than that of MMSE (Zhang *et al.*, 2021). The difference in annual decline rate can better reflect subtle changes in early cognitive function, suggesting that clinical attention should be paid to early optimization of the medication regimen for AD patients to delay the progressive decline of cognitive function.

Table 3: Risk of progression to moderate or severe dementia (CDR ≥2) among patients with mild dementia at baseline (CDR ≤1) [n(%)]

Group	n	CDR progression (baseline score ≤1 to ≥2) (n)	Incidence rate (%)	Risk ratio (RR)	95% Confidence interval	χ^2 Value	*p* Value
Polypharmacy group	119	42	35.3	2.27	1.39-3.70	10.21	0.001
Non-Polypharmacy group	122	19	15.6				

Table 4: Longitudinal changes and annual rate of decline in MoCA scores during the 3-year follow-up (points, x ± s)

Group	n	Baseline	Year 1	Year 2	Year 3	Annual decline rate (points/year)	*p* Value
Polypharmacy group	150	16.4 ± 2.7	15.3 ± 3.2	13.5 ± 3.0	11.2 ± 3.2	1.7 ± 0.6	<0.001
Non-Polypharmacy group	150	16.6 ± 3.0	15.9 ± 3.0	14.9 ± 3.2	13.5 ± 3.4	1.0 ± 0.7	

Table 5: Comparison of fall incidence and all-cause re-hospitalization rates between groups over 3 years [n(%)]

Indicators	Polypharmacy group (n=150)	Non-polypharmacy group(n=150)	Risk ratio (RR)	95% Confidence interval	χ^2 Value	*p* Value
Fall incidence	33 (22.0%)	18 (12.0%)	1.82	1.07 - 3.11	9.49	0.002
All-cause re-admission	75 (50.0%)	45 (30.0%)	1.67	1.25 - 2.22	12.02	<0.001

Table 6: Comparison of 3-year all-cause mortality between the polypharmacy and non-polypharmacy groups [n(%)]

Group	n	Deaths (n)	Mortality rate (%)	Risk ratio (RR)	95% Confidence interval	χ^2 Value	*p* Value
Polypharmacy group	150	22	14.7	1.16	0.80-1.68	0.65	0.42
Non-Polypharmacy group	150	19	12.7				

Table 7: Multivariable logistic regression analysis of factors associated with significant cognitive decline (MMSE reduction ≥3 points) at 3 years

Variable	β	OR (95% CI)	Wald χ^2	*p* Value
High anticholinergic burden (ACB ≥ 3)	0.916	2.5(1.7 - 3.7)	22.14	<0.001
Age (per 1-year increase)	0.020	1.02(0.98 - 1.06)	1.17	0.28
Sex (Male vs. Female)	0.095	1.1(0.7 - 1.7)	0.21	0.65
Baseline MMSE (per 1-point increase)	-0.051	0.95(0.88 - 1.02)	2.07	0.15
Number of comorbidities (≥3 vs. <3)	0.336	1.4(0.9 - 2.2)	2.27	0.13

The incidence of falls and all-cause rehospitalization in the polypharmacy group were significantly higher than that in the non-polypharmacy group. This finding is consistent with established evidence linking polypharmacy to an increased risk of adverse outcomes, including falls, in older adults (Roncal-Belzunce *et al.*, 2024). Its mechanism may be related to adverse reactions such as sedative effect, orthostatic hypotension effect and balance function impairment of drugs (Rasu *et al.*, 2025; Bhanu *et al.*, 2021). AD patients have impaired cognitive function and decreased balance ability and the adverse reactions caused by polypharmacy will further amplify the risk of falls, which may lead to serious complications such as fractures and cerebral hemorrhage, thereby increasing the probability of rehospitalization. In addition, drug interactions caused by polypharmacy and poor treatment effects (such as poor blood pressure and blood glucose control) are also important reasons for increased rehospitalization rates (Govoni *et al.*, 2024). The analysis further revealed no significant intergroup disparity in all-cause mortality. It is hypothesized that the mortality impact of polypharmacy may depend on drug type: essential medications (e.g., cardioprotective or hypoglycemic agents) could lower mortality from underlying conditions, whereas potentially inappropriate medications might increase risk, potentially offsetting each other and resulting in the observed neutral effect on overall mortality (Hayashi *et al.*, 2024). This finding suggests that managing polypharmacy in AD should not focus on indiscriminate "drug reduction." Instead, it necessitates an individualized risk-benefit assessment to optimize medication regimens by precisely deprescribing unnecessary or high-risk drugs while ensuring effective control of underlying conditions. The multivariate logistic regression analysis in this study confirmed that an elevated anticholinergic burden (ACB score ≥3) remained an independent predictor of significant cognitive decline after adjustment for multiple confounders. This is mechanistically plausible, as these drugs exert their

adverse effects by antagonizing central acetylcholine receptors and impaired cholinergic neurotransmission constitutes a core pathological feature of Alzheimer's disease. Therefore, for AD patients, the use of exogenous anticholinergic drugs is tantamount to "adding insult to injury" (Okita *et al.*, 2023). A two-year longitudinal study (Fox *et al.*, 2011), which included 134 participants aged 65 years and older, clearly showed that the use of drugs with anticholinergic activity increased the cumulative risk of cognitive impairment and death. In the complex context of polypharmacy, this study isolated the independent effect of ACB burden through multivariate analysis, strongly suggesting that the cognitive harms of polypharmacy are driven in large part by the anticholinergic drugs it contains. This provides research directions for clinical interventions; firstly, systematic drug review, including ACB assessment, should be established as a standard process in the medical management of elderly AD patients, especially hospitalized patients. A need assessment and risk-benefit rebalancing were performed on the patient's full medication list. Secondly, prescription simplification should not be blindly "reducing the number", but precisely "reducing the load", that is, prioritizing, trying to replace or discontinue those drugs with high ACB scores.

Limitations

Of course, this study has several inherent limitations. First, although PSM was employed in its retrospective design to mitigate confounding bias, the potential influence of unmeasured or unknown factors cannot be entirely ruled out. Secondly, the single-center nature of this study may limit the generalizability of the findings, necessitating validation in future multicenter studies. Third, the operational definition of polypharmacy (concurrent use of ≥5 medications) is quantitative and does not fully capture the qualitative appropriateness of medication regimens, including dosing, duration of use, and the specific risk-benefit profile of individual drugs. Future research should build upon these findings while addressing the aforementioned limitations. Prospective, multicenter cohort studies are needed to establish causality better and elucidate long-term outcomes. Importantly, future studies should incorporate qualitative assessments of medication regimens beyond simple counts. Applying established tools such as the Beers Criteria or the STOPP/START criteria to identify Potentially Inappropriate Medications (PIMs) would provide a more nuanced understanding of medication-related risk. Furthermore, employing structured deprescribing frameworks in intervention studies could help determine not only whether to reduce medications, but also how to do so safely and effectively. This would bridge the gap between identifying polypharmacy as a risk factor and implementing actionable, patient-centered optimization strategies in clinical practice. Additionally, exploring the optimal threshold for polypharmacy in AD and developing frameworks for individualized medication evaluation would provide a more comprehensive evidence base for clinical practice.

CONCLUSION

In summary, this study identified polypharmacy as a significant and independent risk factor for 3-year cognitive deterioration, CDR progression, falls and rehospitalization in hospitalized older adults with Alzheimer's disease, with the risk being further heightened by a higher anticholinergic burden. These findings support the clinical importance of medication optimization through structured medication review and deliberate deprescribing. Implementing such strategies could help attenuate cognitive decline, reduce adverse events and potentially improve long-term outcomes in this vulnerable population.

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Authors' contributions

Youchao Hu: Developed and planned the study, performed experiments and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions; Jianping Jiang and Genming Shen: Participated in collecting, assessing and interpreting the date. Made significant contributions to date interpretation and manuscript preparation; Xiaojie Ding: Provided substantial intellectual input during the drafting and revision of the manuscript.

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Data availability statement

All data generated or analysed during this study are included in this published article [and its supplementary information files]. [Only use this if all data is in the manuscript or supplementary files].

Ethical approval

This study received ethics approval from the Ethics Committee of The Third Affiliated Hospital of Jiaxing University (Zhejiang Rongjun Hospital) (Approval No. JX--Y20210918), in compliance with the Declaration of Helsinki and international standards for medical research ethics. Given the retrospective study design, the analysis was based on previously archived clinical data, and the ethics committee approved an exemption from informed consent. All data were anonymized to protect participant confidentiality. This study was performed in adherence with the STROBE guidelines. See Supplementary file for the STROBE checklist.

Conflicts of interest

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

Supplementary data

https://www.pjps.pk/uploads/2026/04/SUP1775374330.pdf

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