Drugs - Real World Outcomes (2025) 12:437–446
https://doi.org/10.1007/s40801-025-00509-7

ORIGINAL RESEARCH ARTICLE

CALS and ACB Scales are Associated with Physical and Cognitive Impairment and Predict Mortality in Nursing Home Residents

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Accepted: 16 July 2025 / Published online: 26 July 2025

Abstract

Background and Objective Anticholinergic medications are known to affect the prognosis of older nursing home residents. Various anticholinergic scales were developed to measure the cumulative anticholinergic burden; among them, the CRID-ECO Anticholinergic Load Scale (CALS) has recently emerged as a new tool to identify patients with cognitive impairment due to anticholinergic burden. This study aimed to externally validate the CALS and to evaluate the association of CALS and the anticholinergic cognitive burden (ACB) scales with baseline cognitive and functional impairment, as well as with 3-year mortality rates.

Methods A prospective cohort of 600 nursing home residents (mean age 80.4 ± 8.0 years; 69.8% women) underwent a comprehensive geriatric assessment. Anticholinergic burden was assessed at baseline using both CALS and ACB scales. Cognitive impairment (Mini-Mental State Examination < 24) and physical disability (one or more impaired activities of daily living) were evaluated cross-sectionally using a logistic regression model. Cox proportional hazards models were used to estimate the association between anticholinergic burden and 3-year mortality, adjusting for age, sex, multimorbidity, nutritional status, and cognitive and functional status.

Results Among 600 nursing home residents included in the study, 72.0% had cognitive impairment and 56.3% had at least one activity of daily living limitation. The CALS and ACB scores were significantly correlated ($\rho = 0.76$), but CALS identified a higher number of residents with moderate-to-high anticholinergic burden. Multivariate logistic regression showed that CALS ≥ 2 was independently associated with cognitive impairment (odds ratio 1.84, 95% confidence interval 1.02–3.34), whereas ACB ≥ 2 was not. Both scales were associated with activities of daily living disability, with a stronger gradient and better goodness of fit for CALS than ACB. During the 3-year follow-up, 25.3% of residents died. Cox regression analyses showed that residents with CALS or ACB ≥ 2 had significantly lower survival over 3 years. In fully adjusted Cox models, both CALS ≥ 2 (hazard ratio 1.93, 95% confidence interval 1.07–3.46) and ACB ≥ 2 (hazard ratio 1.69, 95% confidence interval 1.02–2.83) remained associated with increased mortality. Prognostic performance was similar (CALS C-index: 0.783; ACB: 0.781), but the model fit favored CALS.

Conclusions In this cohort of nursing home residents, anticholinergic burden as measured by both CALS and ACB was associated with baseline physical impairment and 3-year mortality, but CALS showed a better goodness of fit. Between the two scales, CALS only was independently associated with baseline cognitive impairment. These findings support the clinical utility of CALS in assessing anticholinergic-related risk among frail older adults in institutional settings.

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Key Points

Anticholinergic burden is a significant risk factor in older adults, contributing to cognitive impairment, physical disability, and mortality.

The CRIDECO Anticholinergic Load Scale includes a broader range of medications and may better capture anticholinergic-related risks than the anticholinergic cognitive burden scale.

This study assesses the validity of the CRIDECO Anticholinergic Load Scale in nursing home residents by comparing its associations with cognitive/physical impairment and 3-year mortality against those of the anticholinergic cognitive burden scale.

1 Introduction

Anticholinergic burden, the cumulative effect of using one or multiple drugs with anticholinergic activity, is frequently found among nursing home residents (NHRs). This burden is associated with several adverse events, including cognitive impairment, frailty, urinary retention, and increased mortality [1–5]. To assess the anticholinergic burden and the risk of anticholinergic side effects in older people, various scales have been employed. Among them, the anticholinergic cognitive burden (ACB) scale has gained attention because of several studies in hospitalized older patients reporting associations with cognitive, functional decline, and mortality [4, 6–8]. Recently, Ramos et al. developed and validated the CRIDECO Anticholinergic Load Scale (CALS) as a promising indicator of subtle cognitive impairment [9]; for this reason, it emerged as a new risk tool in patients with dementia and Parkinson's disease [10], and mortality and poor outcomes among older inpatients with pneumonia [11]. Recently, Novella et al. found CALS to have the best model fit out of 20 anticholinergic scales in the cross-sectional association with cognitive impairment and physical disability among older inpatients [12]. Given the vulnerability of NHRs**,** a population marked by cognitive and functional disability, polypharmacy, renal impairment, and a risk of high anticholinergic burden [13–17], CALS may offer a valuable alternative to traditional scales such as ACB. However, its utility in this setting remains underexplored. For this reason, we performed a cross-sectional and longitudinal analysis to (a) validate the CALS score as a tool to measure anticholinergic burden among NHRs; (b) investigate the cross-sectional association of CALS and ACB scales with cognitive and physical impairment; and (c) assess the accuracy of the ACB scale and CALS in predicting mortality in this population.

2 Methods

2.1 Sample

All patients consecutively admitted to ten participating nursing homes were invited to take part in the study. A total of 868 patients aged 65 years and older were initially screened and enrolled between January 2018 and May 2019 and followed up over a 36-month period. After obtaining a written informed consent from all participants enrolled in the study or their legal representatives, all recruited NHRs underwent a standardized multidimensional geriatric assessment, including detailed clinical history, anthropometric measurements, and validated instruments to evaluate cognitive function, functional status, physical performance, nutritional condition, and depressive symptoms. Routine hematological tests were also performed. Patients were followed up every 12 months for 3 years to collect information on their vital status. In the case of discharged NHRs, this information was collected via a telephone interview with residents and/or their relatives/caregivers. For patients who died during the follow-up period, information about the date, place, and cause of death was collected from death certificates provided by relatives or caregivers. For the current analysis, patients with missing data on baseline cognitive and physical function ($n = 170$) or missing mortality data ($n = 98$) were excluded, leaving 600 patients to be included in the analyses. The study design was approved by the Regional Ethics Committee of Catanzaro, Italy (protocol CE 119/2016) and was performed in accordance with the standards of ethics outlined in the Declaration of Helsinki.

2.2 Exposure Variables

Anticholinergic burden was assessed using two different scales: ACB [18] and CALS [9], which include 88 and 217 anticholinergic medications, respectively. The ACB scale was developed to assess the extent of anticholinergic adverse effects on cognitive function [18] and is considered particularly accurate in the assessment of central anticholinergic burden [19] compared to other tools mainly focused on peripheral effects [20, 21]. Although the ACB scale is well established, it may underestimate anticholinergic effects from newer or commonly used drugs in NHRs. CALS, derived from a more recent literature review, includes a broader array of anticholinergic agents and may better reflect the contemporary medication landscape in NHRs. Indeed, the CALS was recently

developed by Ramos et al. [9] after performing a systematic review of the literature and comparing anticholinergic medications included in seven other scales; in brief, the CALS list includes 217 anticholinergic medications classified according to their potency in three classes: (a) drugs with low anticholinergic potency (score = 1; 125 medications); (b) drugs with medium anticholinergic potency (score = 2; 28 medications); and (c) drugs with high anticholinergic potency (score = 3; 62 medications). The cumulative CALS score was calculated by summing all the burden scores for each drug taken by the patient.

The main exposure variable was calculated as follows: ACB or CALS score = 0 (no anticholinergic medications); ACB or CALS score = 1 (low anticholinergic burden); ACB or CALS scores ≥ 2 (moderate-to-high anticholinergic burden) [22]. Anticholinergic burden was assessed at baseline only, as repeat assessments were not available. However, medication regimens in NHRs tend to remain stable over time because of long-term prescribing patterns and limited therapeutic changes in this setting [23].

2.3 Outcomes

The primary aim of the study is to evaluate the cross-sectional association between anticholinergic burden and both physical and cognitive impairment. These outcomes were assessed through a comprehensive geriatric assessment, which was performed systematically by trained personnel at the baseline visit, using the interRAI long-term care facility instrument. Physical functioning was evaluated by assessing the capacity to perform five activities of daily living (ADLs, i.e., bathing, dressing, eating, toileting, and transfer) using a modified version of the Katz Index [24]. Each activity was scored as 0 if patients were unable to perform the task and 1 for patients able to perform such activity. Then, ADL scores ranged between 0 (unable to perform any activity) and 5 (able to perform all the activities). Cognitive status was assessed using the age- and education-adjusted Mini-Mental State Examination (MMSE) score [25], and patients scoring less than 24 were considered cognitively impaired [26].

The secondary aim of the study was to investigate the association between anticholinergic burden and mortality during the follow-up. For participants who died during the follow-up period, information about the date, place, and cause of death was collected from death certificates provided by relatives or caregivers. Patients who were lost to follow-up or discharged from the nursing home were censored at the time of their last known contact.

2.4 Covariates

Covariates for cross-sectional analyses included a history of chronic diseases and nutritional status. The latter was evaluated using the Mini Nutritional Assessment (MNA), a well-validated tool for assessing malnutrition in elderly individuals [27]. A score lower than 12 points indicates the presence of malnutrition/malnutrition risk [28]. A history of chronic diseases was also detailed; for the present analyses, we considered hypertension, atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure (CHF), coronary artery disease (CAD), peripheral artery disease (PAD), stroke, dementia, anemia, and chronic kidney disease. Overall comorbidity was assessed by the Cumulative Illness Rating Score for Geriatrics (CIRS-G) [29]. The presence of anemia was defined as having a hemoglobin level < 12 g/dL among women and < 13 g/dL among men.

2.5 Statistical Analysis

Demographic, clinical characteristics, and outcomes data were summarized with counts and percentages for categorical variables, and means (standard deviation) for normally distributed continuous variables. The Kolmogorov–Smirnov test was used to check the normality of the related variables. An independent sample t-test and chi-squared test were used when appropriate. The concordance between the two anticholinergic scales was measured by using Spearman's ρ coefficient. A logistic regression analysis was used to test the relationship between anticholinergic burden and the prevalence of cognitive impairment (MMSE < 24) and disability in at least one ADL; the strength of the association was expressed by estimating the odds ratio (OR) and 95% confidence interval (CI). Regression models were corrected for potential confounders as follows:

Model A: age and sex adjusted;

Model B: model A + MNA Short Form and CIRS-G;

Model C: model B but with the number of non-anticholinergic drugs and with chronic diseases (hypertension, atrial fibrillation, diabetes, CHF, CAD, PAD, stroke, dementia, anemia, chronic obstructive pulmonary disease, and chronic kidney disease) instead of CIRS-G.

A Kaplan–Meier analysis was performed to estimate survival curves stratified for anticholinergic burden, quantified using both the ACB scale and CALS. The relationship between anticholinergic burden and 3-year mortality was assessed by bivariate and multivariate Cox regression models, including the same confounders used in cross-sectional analyses with the addition of MMSE and dependent ADL. Supplementary analyses were repeated for 1- and 2-year mortality. The length of survival from the baseline visit until death was used as the failure time for the models. Survivors were censored on the day of the last follow-up visit. The

proportional hazard assumption was checked graphically, plotting the log-minus-log survival function over time. The performance of these models was assessed by computing the cross-validated ten-fold concordance index [30].

To limit the risk of confounding by indication—where certain medications may be prescribed because of underlying conditions associated with poor outcomes—we repeated the analyses by (a) grouping patients with no or minimal anticholinergic exposure (scores of 0 or 1) together and compared them to those with higher exposure (scores ≥ 2). This approach helps distinguish the effects of significant anticholinergic burden from those of mild or incidental exposure; (b) stratifying survival models in patients with and without specific disease conditions.

Statistical analyses were performed using the survival package of R v3.4.2 statistical language.

3 Results

3.1 Descriptive Characteristics of the Study Population

The clinical characteristics of the whole sample of 600 patients, as well as those of the subgroups surviving and deceased patients are reported in Table 1. Overall, these residents received 5096 medications, which were considered for this analysis. Approximately 69.8% of the sample were female (Table 1), and the mean (standard deviation) age was 80.4 (8.0) years. The study population was treated with 6.3 (3.3) medications. Eight residents did not receive any medication at all. Polypharmacy was found in 73.37% of the study population, while excessive polypharmacy (> 10) was found in 14.45%.

Despite the two anticholinergic scales were strongly correlated (Spearman's ρ: 0.76, $p < 0.001$), the CALS score was higher than the ACB score; furthermore, patients with two or more anticholinergic medications were almost 50% according to CALS and 22% according to ACB. After calculating the difference between CALS and ACB scores, we observed that 56% of the study population had the same score, only a minority had an ACB greater than the CALS score, while 41% of individuals had a higher CALS score than the ACB score. The list of drugs included in the ACB scale and CALS along with their distribution at hospital admission in the study population are reported in Tables 1 and 2 of the Electronic Supplementary Material (ESM).

During the 3-year follow-up, 152 out of 600 patients died, with a mortality rate of 25.3%. Patients who died during the follow-up were older, predominantly men, with a very high prevalence of physical disability, cognitive impairment, and malnutrition, and a high multimorbidity burden ($p < 0.001$); furthermore, atrial fibrillation, CHF, CAD, PAD, stroke, dementia, and anemia were more common in deceased individuals compared with survivors. Deceased subjects also had a higher anticholinergic burden compared with survivors; more specifically, patients who died took more commonly two or more anticholinergic medications compared with survivors.

Characteristics of the study population stratified by anticholinergic groups (0, 1 and 2 or more anticoholinergic score), identified by the ACB scale and CALS were reported in Table 3 of the ESM. Comparing the three groups, patients with higher scores were characterized by older age, a greater prevalence of ADL impairment, cognitive impairment, and malnutrition, and a higher CIRS-G score compared with those with lower scores; furthermore, increasing anticholinergic scores were associated with a higher prevalence of atrial fibrillation, CHF, PAD, dementia, anemia, and chronic kidney disease.

3.2 Cross-Sectional Association Between Anticholinergic Burden, Physical Disability, and Cognitive Impairment

The association of both continuous or categorical CALS and ACB scales with ADL and cognitive impairment is shown in Table 2. A CALS score of two or more was associated with cognitive impairment in both bivariate (OR 2.46, 95% CI 1.53–3.99) and multivariate models (OR 2.19, 95% CI 1.29–3.74 for model B and OR 1.84, 95% CI 1.02–3.34 for model C). This association was not significant when considering ACB categories instead of CALS categories. In contrast, an association with ADL impairment was constantly observed with both scales, but a graded increase in the strength of association with increased anticholinergic use was evident only with CALS (Table 2); the model including CALS showed a better goodness of fit than ACB (AIC: 406.7 vs 408.2; BIC: 477.4 vs 479.0). Analyses on continuous scales confirmed all study findings.

Finally, to evaluate how the discordance between the two scales relates to the prevalence of ADL and cognitive impairment, we calculated the difference between the two scores and created a categorical variable to represent this discordance: interestingly, having a CALS score greater than the ACB score was associated with both cognitive impairment and ADL disability compared to patients with concordant scores or with an ACB score less than the CALS score (Table 2).

3.3 Impact of Anticholinergic Burden on Survival

Kaplan–Meier survival functions of nursing home patients according to CALS and ACB categories are shown in Fig. 1. Patients with ACB scores ≥ 2 exhibited the lowest survival probability during the follow-up period ($p < 0.0001$, panel

Table 1 Sociodemographic and clinical characteristics of the study population and of survived and deceased patients

	Total ($N = 600$)	Survived ($N = 448$)	Deceased ($N = 152$)	*P*-value
Age, years, mean (SD)	80.1 (8.0)	78.2 (7.4)	85.5 (7.3)	<0.001
Female sex, *n* (%)	419 (69.8)	311 (69.4)	108 (71.1)	0.782
Dependent ADL, mean (SD)	1.8 (1.9)	1.3 (1.7)	3.2 (1.6)	<0.001
Dependency ≥ 1 ADL, *n* (%)	338 (56.3)	200 (44.6)	138 (90.8)	<0.001
MMSE (mean, SD)	19.2 (6.4)	20.5 (5.9)	15.2 (6.2)	<0.001
Cognitive impairment, *n* (%)	432 (72.0)	290 (64.7)	142 (93.4)	<0.001
MNA-SF, mean (SD)	11.5 (2.8)	12.0 (2.8)	10.0 (2.4)	<0.001
Hypertension, *n* (%)	442 (74.7)	327 (74.3)	115 (75.7)	0.826
Atrial fibrillation, *n* (%)	67 (11.3)	39 (8.9)	28 (18.4)	<0.001
Diabetes mellitus, *n* (%)	179 (30.2)	127 (28.9)	52 (34.2)	0.256
COPD, *n* (%)	131 (22.1)	90 (20.5)	41 (27.0)	0.120
CHF, *n* (%)	39 (6.6)	16 (3.6)	23 (15.1)	<0.001
CAD, *n* (%)	150 (25.3)	100 (22.7)	50 (32.9)	0.017
PAD, *n* (%)	150 (25.3)	81 (18.4)	69 (45.4)	<0.001
Stroke, *n* (%)	47 (7.9)	24 (5.5)	23 (15.1)	<0.001
Dementia, *n* (%)	150 (25.3)	81 (18.4)	69 (45.4)	<0.001
Anemia, *n* (%)	243 (42.3)	162 (37.9)	81 (54.7)	<0.001
CKD, *n* (%)	42 (7.1)	18 (4.1)	24 (15.8)	<0.001
CIRS-G score, mean (SD)	13.2 (11.1)	11.0 (9.4)	19.6 (13.1)	<0.001
Number of medications, mean (SD)	6.8 (3.3)	6.4 (3.1)	8.0 (3.3)	<0.001
ACB score, mean (SD)	0.9 (1.3)	0.8 (1.2)	1.3 (1.4)	<0.001
ACB = 0, *n* (%)	316 (52.7)	259 (57.8)	57 (37.5)	
ACB = 1, *n* (%)	150 (25.0)	112 (25.0)	38 (25.0)	
ACB ≥ 2, *n* (%)	134 (22.3)	77 (17.2)	57 (37.5)	
CALS score, mean (SD)	1.6 (1.7)	1.4 (1.6)	2.2 (1.8)	
CALS = 0, *n* (%)	202 (33.7)	174 (38.8)	28 (18.4)	
CALS = 1, *n* (%)	140 (23.3)	110 (24.6)	30 (19.7)	
CALS ≥ 2, *n* (%)	258 (43.0)	164 (36.6)	94 (61.8)	
Discordance, *n* (%)				0.008
ACB < CALS	246 (41.0)	169 (37.7)	77 (50.7)	
ACB > CALS	15 (2.5)	14 (3.1)	1 (0.7)	
ACB = CALS	339 (56.5)	265 (59.2)	74 (48.7)	

ACB anticholinergic cognitive burden, *CAD* coronary artery disease, *CALS* CRIDECO Anticholinergic Load Scale, *CHF* congestive heart failure, *CIRS-G* Cumulative Illness Rating Score for Geriatrics, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *MMSE* Mini-Mental State Examination, *MNA-SF* Mini Nutritional Assessment, Short Form, *PAD* peripheral artery disease, *SD* standard deviation

A). This association was replicated when the anticholinergic burden was assessed by means of the CALS score. Cox regression models investigating the association between anticholinergic scales and mortality confirmed these preliminary results (Table 3). Increasing anticholinergic scores were associated with long-term mortality in both bivariate and multivariate Cox regression models. In particular, a CALS or ACB score ≥ 2 was associated with increased mortality compared with individuals not receiving any anticholinergic medications. Prognostic accuracy in relation to overall mortality was similar for both scales; indeed, a cross-validated concordance index was nearly identical (ACB: 0.781, 95% CI 0.746–0.817; CALS: 0.783, 0.746–0.820); however, CALS showed a better goodness of fit (AIC: 1102.9; BIC: 1151.8) compared with ACB (AIC: 1103.7, BIC: 1152.7). When compared to patients with 0–1 anticholinergic scores, only CALS ≥ 2 remained significantly associated with the outcome (Table 4 of the ESM). Sensitivity analyses were conducted in subgroups of patients without some chronic diseases: CALS ≥ 2 was significantly associated with mortality in patients with diabetes and dementia, and in those without CAD or CHF ($p < 0.001$). Supplementary analyses were conducted to evaluate the association between anticholinergic scales and 1- and 2-year mortality (Tables 5 and 6 of the ESM); in brief, while a continuous CALS score was significantly associated with both 1- and 2-year mortality,

Table 2 ORs for the relationship between anticholinergic burden as assessed by the ACB and scale and CALS and either cognitive or physical impairment at the baseline visit

MMSE < 24	Model A, OR (95% CI)	Model B, OR (95% CI)	Model C, OR (95% CI)
Continuous ACB	–	–	–
ACB 0 (reference)	–	–	–
ACB 1	1.28 (0.79–2.10)	1.08 (0.64–1.85)	0.96 (0.54–1.74)
ACB 2 or more	2.03 (1.16–3.67)	1.90 (1.02–3.67)	1.35 (0.67–2.77)
Continuous CALS	1.38 (1.20–1.61)	1.33 (1.14–1.58)	1.23 (1.04–1.50)
CALS 0 (reference)	–	–	–
CALS 1	1.09 (0.66–0.81)	1.06 (0.61–1.85)	1.14 (0.62–2.09)
CALS 2 or more	2.46 (1.53–3.99)	2.19 (1.29–3.74)	1.84 (1.02–3.34)
CALS < ACB	–	–	–
CALS ≥ ACB	1.97 (1.29–3.02)	1.82 (1.15–2.92)	1.78 (1.07–2.99)
At least 1 disabled ADL			
Continuous ACB	1.72 (1.44–2.08)	1.54 (1.27-1.89)	1.38 (1.11–1.74)
ACB 0 (reference)	–	–	–
ACB 1	3.45 (2.16–5.60)	3.28 (1.90–5.75)	3.16 (1.71–5.94)
ACB 2 or more	4.13 (2.48–7.03)	3.01 (1.67–5.53)	2.45 (1.23–4.92)
Continuous CALS	1.72 (1.49–2.00)	1.58 (1.35–1.87)	1.47 (1.23–1.80)
CALS 0 (reference)	–	–	–
CALS 1	2.09 (1.27–3.46)	2.03 (1.14–3.66)	2.45 (1.25–4.86)
CALS 2 or more	4.92 (3.14–0.82)	3.93 (2.31–6.80)	3.73 (1.98–7.16)
CALS-ACB < 1	–	–	–
CALS-ACB ≥ 1	1.99 (1.36–2.95)	1.64 (1.05–2.59)	1.56 (0.92–2.65)

ACB anticholinergic cognitive burden, *ADL* activity of daily living, *CALS* CRIDECO Anticholinergic Load Scale, *CI* confidence interval, *Model A* age and sex-adjusted, *Model B* Model A + Mini Nutritional Assessment, Short Form and Cumulative Illness Rating Score for Geriatrics, *Model C* model B + chronic diseases (hypertension, atrial fibrillation, diabetes mellitus, congestive heart failure, coronary artery disease, peripheral artery disease, stroke, dementia, anemia, chronic obstructive pulmonary disease, and chronic kidney disease) instead of Cumulative Illness Rating Score for Geriatrics + number of not anticholinergic medications

Table 3 Cox proportional hazard models investigating the relationship between anticholinergic burden as assessed by the ACB scale and CALS and 3-year mortality during the follow-up

	Model A, HR (95% CI)	Model B, HR (95% CI)	Model C, HR (95% CI)
Continuous ACB	1.16 (1.05–1.29)	1.16 (1.02–1.31)	1.10 (0.96–1.26)
ACB 0 (reference)	–	–	–
ACB 1	1.41 (0.93–2.14)	1.62 (0.99–2.61)	1.45 (0.89–2.83)
ACB 2 or more	2.11 (1.45–3.08)	1.94 (1.23–3.06)	1.69 (1.02–2.83)
Continuous CALS	1.16 (1.08–1.25)	1.11 (1.02–1.21)	1.09 (1.01–1.21)
CALS 0 (reference)	–	–	–
CALS 1	1.77 (1.05–2.98)	2.05 (1.12–3.76)	1.58 (0.82–3.02)
CALS 2 or more	2.56 (1.66–3.94)	2.37 (1.39–4.03)	1.93 (1.07–3.46)
CALS-ACB < 1	–	–	–
CALS-ACB ≥ 1	1.11 (1.09–1.14)	1.27 (0.87–1.85)	1.20 (0.80–1.80)

ACB anticholinergic cognitive burden, *CALS* CRIDECO Anticholinergic Load Scale, *CI* confidence interval, *HR* hazard ratio, *Model A* age and sex adjusted, *Model B* Model A + Mini Nutritional Assessment, Short Form, Cumulative Illness Rating Score for Geriatrics, dependent activities of daily living, and Mini-Mental State Examination, *Model C*: model B + chronic diseases (hypertension, atrial fibrillation, diabetes mellitus, congestive heart failure, coronary artery disease, peripheral artery disease, stroke, dementia, anemia, chronic obstructive pulmonary disease, and chronic kidney disease) instead of Cumulative Illness Rating Score for Geriatrics + number of not anticholinergic medications

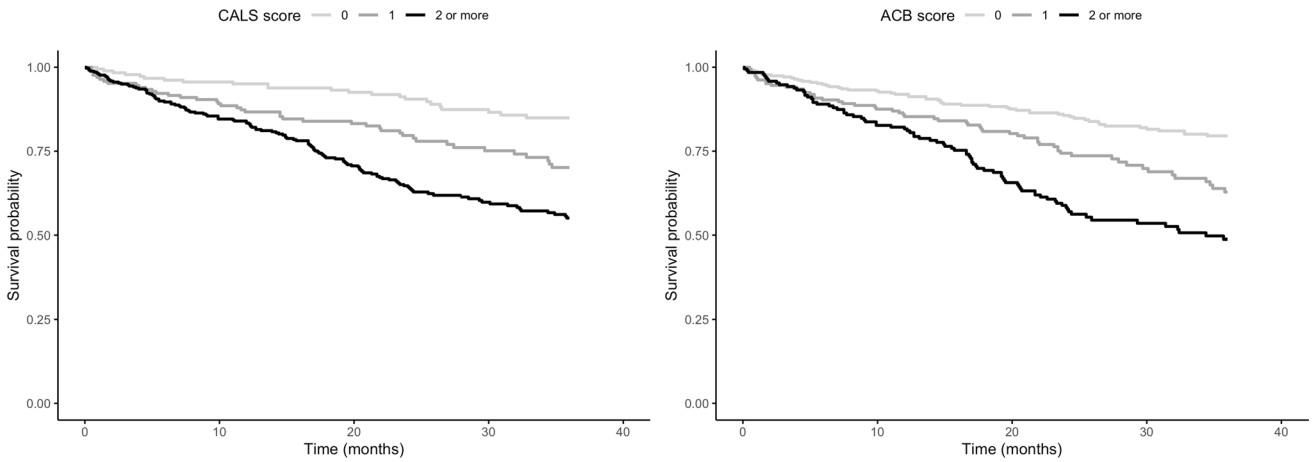

Fig. 1 Kaplan–Meier survival functions of nursing home residents according to the anticholinergic cognitive burden (ACB) and CRIDECO Anticholinergic Load Scale (CALS)

the association between CALS classes and both continuous and categorical ACB became significant only after 2 years.

4 Discussion

In this prospective cohort study, we found that anticholinergic burden, as measured through CALS and ACB, was associated with ADL impairment and 3-year mortality, while CALS only was associated with cognitive impairment, thus corroborating previous evidence that showed the higher number of medications impacting cognitive function included in this scale compared with ACB [9, 12]; furthermore, a difference of ≥1 between CALS and ACB was also associated with cognitive impairment, even after adjusting for ADL impairment and multimorbidity.

To our knowledge, this is the first real-world study to assess the validity of CALS as a tool to measure anticholinergic burden among NHRs, evaluate its association with cognitive impairment, and its ability to predict long-term survival. This is particularly relevant in the population of NHRs, who are characterized by high levels of clinical complexity and cognitive dysfunction [15, 16]. Previous studies have linked anticholinergic burden with the risk of cognitive decline, dementia [31, 32], and mortality [33] among older individuals. Many commonly used medications in geriatric settings have anticholinergic properties, despite awareness of their harm being not always found among physicians and pharmacists [34, 35]. Nursing home residents represent a segment of the geriatric population at an increased risk of anticholinergic drug use, most commonly antipsychotics, antidepressants, and opioids [36]. The cumulative muscarinic inhibition due to anticholinergic load may trigger the onset of multiple cardiovascular and neurological side effects that may also lead to death. However, the definition of anticholinergic burden is challenging because of the heterogeneity and poor agreement among existing scales designated to measure the burden [37]; among the most recent tools to evaluate anticholinergic burden, CALS has been developed and validated after an extensive systematic literature review and was shown to be particularly sensitive to identify the impact of anticholinergic medications on cognitive function [9]; this finding has been confirmed in our population where both scales were associated with ADL impairment, but only CALS was significantly associated with cognitive impairment; it is likely that the greater anticholinergic inclusivity of CALS compared with the ACB scale may contribute to this finding.

With regard to the relationship with mortality, a few studies have shown that high anticholinergic use can increase the risk of poor outcomes in older institutionalized individuals; indeed, a previous cohort study on 1490 Italian NHRs has shown that anticholinergic burden measured by the Anticholinergic Risk Scale may be associated with an increased risk of falls, functional decline, and cognitive impairment [38]; in another study on 3761 NHRs, high ACB scores were associated with an increased risk of 5-year mortality [39]. In our cohort, increasing CALS and ACB scores predicted mortality at 3 years with comparable and good prognostic accuracy. The association with mortality remained statistically significant also after correcting for functional and cognitive impairment, which are known to be the strongest predictors of poor survival in this population. Stratified analyses showed that such associations were particularly strong among patients with dementia and in those with diabetes; indeed, anticholinergic burden may exacerbate some diabetic complications, such as cardiovascular issues (e.g., accelerated heart rate, arrhythmias) and glycemic dysregulation [40, 41], thus increasing the risk of death; furthermore, both patients with dementia and diabetes have poorer

cognitive reserve [42], which may contribute to increased vulnerability to anticholinergic central side effects, with worsening of cognitive decline [43] and increased risk of falls and mortality. For this reason, periodical monitoring and revision of drug regimens in older NHRs may be useful to detect patients at risk of anticholinergic side effects; clinical practice guidelines and the 2023 Beers Criteria now recommend deprescribing or tapering potentially harmful medications, such as benzodiazepines and first-generation antipsychotics. Similarly, when treating depressive disorders, clinicians should prioritize prescribing antidepressants with minimal anticholinergic effects, such as sertraline, over those with higher anticholinergic potential, such as paroxetine. However, it is worthy of note that, in this study, a moderate-to-high anticholinergic burden has been associated with increased mortality even in patients without chronic diseases such as CHF and CAD; this finding underlines the importance of revising drug regimens and addresses anticholinergic burden in NHRs independent of the presence of specific diseases.

Our study has many strengths. First, it enrolled a real-world population of older NHRs, which were followed up for more than 3 years; second, patients underwent a thorough comprehensive geriatric assessment that allowed us to reliably detect functional and cognitive impairment, as well as a thorough pharmacological assessment; third, anticholinergic burden was measured using two scales that were developed after an extensive literature review; however, we acknowledge some limitations. First, the possibility of prevalent user bias cannot be excluded. As medication exposure was assessed at a single timepoint, individuals who tolerated anticholinergic medications without apparent adverse effects may have been more likely to remain on them, potentially underestimating associations with negative outcomes; second, we cannot measure the Drug Burden Index [44], a pharmacokinetically informed tool that has shown high predictive validity in many geriatric cohorts, as its calculation requires detailed data on individual drug dosages and administration regimens. However, this level of precision is often unavailable in retrospective or registry-based studies and is particularly challenging in real-world nursing home datasets, where medication dosing and adherence can vary widely. Additionally, the Drug Burden Index primarily emphasizes sedative and anticholinergic effects combined, which may limit its specificity when isolating the impact of anticholinergic medications alone [44]. In contrast, CALS offers broader drug inclusivity, easier implementation with prescription-level data, and a specific focus on anticholinergic exposure. Third, although we adjusted for multimorbidity using the CIRS-G and included key chronic conditions in our models, we were unable to fully account for the severity of individual comorbidities. While adjustments for major clinical indications and stratified analyses were conducted, residual confounding cannot be excluded, as patients with more severe illnesses are both more likely to receive anticholinergic medications and more likely to experience poor outcomes regardless of drug exposure. Future longitudinal studies with repeated assessments and mediation analyses are needed to address these issues comprehensively.

5 Conclusions and Implications

Increasing anticholinergic burden was associated with cognitive and physical impairment, as well as 3-year mortality among older NHRs. CALS outperformed the ACB scale in the observed associations. These findings support the use of CALS as a clinically relevant tool for assessing anticholinergic-related cognitive risk in institutionalized older adults, while also reinforcing the broader need for cautious prescribing in this vulnerable population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-025-00509-7.

Acknowledgments We acknowledge co-funding from Next Generation EU, in the context of the National Recovery and Resilience Plan, Investment PE8 - Project Age-It: "Ageing Well in an Ageing Society". This resource was co-financed by the Next Generation EU [DM 1557 11.10.2022]. The work has been made possible by the collaboration with Gruppo Baffa (Sadel Spa, Sadel San Teodoro srl, Sadel CSsrl, Casa di Cura Madonna dello Scoglio, AGI srl, Casa di Cura Villa del Rosario srl, Savelli Hospital srl) and Casa di Cura Villa Ermelinda in the frame of the agreements TECNOLOGIE AVANZATE PER IL MIGLIORAMENTO DEI SERVIZI ALLA PERSONA and TECNOLOGIE AVANZATE PER L'INDAGINE DELLE RELAZIONI TRA UOMO ED AMBIENTI DI VITA.

Declarations

Funding This study was funded by Next Generation EU [DM 1557 11.10.2022], in the context of the National Recovery and Resilience Plan, Investment PE8 - Project Age-It: "Ageing Well in an Ageing Society". The funders played no role in the design, execution, analysis and interpretation of the data, or writing of the study.

Conflicts of Interest/Competing Interests Luca Soraci, Ersilia Paparazzo, Mirella Aurora Aceto, Francesco Bruno, Teresa Serra Cassano, Davide Lagrotteria, Salvatore Claudio Cosimo, Pierluigi Mercatante, Francesco Morelli, Maria Princiotto, Andrea Corsonello, Giuseppe Passarino, and Alberto Montesanto have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval This study was approved by the Regional Ethics Committee of Catanzaro, Italy (protocol CE 119/2016).

Consent to Participate Informed written consent was signed by all participants enrolled in the study or their legal representatives.

Consent for Publication Not applicable.

Availability of Data and Material The datasets generated and analyzed during the current study are not publicly available because of institutional and ethical restrictions related to the privacy of NHRs. However, de-identified data may be available from the corresponding author upon reasonable request and with appropriate ethical approval.

Code Availability Not applicable.

Authors' Contributions Conceptualization: LS, EP, and AM; methodology: LS, EP, and AM; formal analysis: LS, E.P., MAA, and AM; data curation: EP, MAA, FB, TSC, SG, FM, and AM; investigation: LS, EP, and AM; writing (original draft preparation): LS, EP, and AM; writing (review and editing): LS, MAA, FB, TSC, SG, SCC, PM, FM, MP, and AM; supervision: AC, GP; funding acquisition: GP. All authors have read and agreed to the published version of the manuscript.

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