

The excess mortality risk associated with anticholinergic burden among older patients discharged from acute care hospital with depressive symptoms

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ABSTRACT

Background: The relationship between anticholinergic burden and mortality is controversial, and the impact of anticholinergic burden on prognosis may vary in presence of other conditions common in old age. We aimed at investigating the role of depressive symptoms as potential effect modifiers in the association between anticholinergic burden and 1-year mortality in older patients discharged from hospital.

Methods: Our series consisted of 576 older patients consecutively admitted to seven geriatric and internal medicine acute care wards in the context of a prospective multicenter observational study. Overall anticholinergic burden was assessed by Anticholinergic Cognitive Burden (ACB) score. Depressive symptoms were assessed by 15-item Geriatric Depression Scale (GDS). The study outcome was all-cause mortality during 12-months follow-up. Statistical analysis was carried out by Cox regression analysis.

Results: After adjusting for potential confounders, discharge ACB score = 2 or more was significantly associated with the outcome among patients with GDS > 5 (HR = 3.70; 95%CI = 1.18–11.6), but not among those with GDS ≤ 5 (HR = 2.32; 95%CI = 0.90–6.24). The association was confirmed among depressed patients after adjusting for ACB score at 3-month follow-up (HR = 3.58; 95%CI = 1.21–10.7), as well as when considering ACB score as a continuous variable (HR = 1.42; 95%CI = 1.10–1.91). The interaction between ACB score at discharge and BADL dependency was statistically significant ($p < .005$).

Conclusions: ACB score at discharge may predict mortality among older patients discharged from acute care hospital carrying high GDS score. Hospital physician should be aware that prescribing anticholinergic medications in such a vulnerable population may have negative prognostic implications.

1. Introduction

Anticholinergic medications are known to cause several side effects and negative outcomes among older patients, including functional decline, falls and delirium [1,2], cognitive impairment [3] and disability [4]. Despite this, the prevalence of anticholinergic use in older patients ranges from 8% to 37% [5].

Reason why the impact of anticholinergic medications on mortality is controversial. A significant increase in risk of death in relation to anticholinergic burden was observed in the general population [6],

among patients discharged from hospital after hip fracture [7], among older people living at home and in institutions [8], as well as among nursing home residents [9] and patients discharged from acute care hospital [10]. However, other studies failed to find significant associations between anticholinergic burden and mortality in hospitalized patients [11], nursing home [1,12] or long term care residents [13]. Furthermore, the impact of anticholinergic burden on prognosis may vary in the presence of other conditions common in old age. Indeed, by using data from the CRiteria to assess Inappropriate Medication use among Elderly complex patients (CRIME) study we recently

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demonstrated that cognitive impairment, history of falls and dependency in BADL are important potential effect modifiers in the association between anticholinergic burden and 1-year mortality in a population of older patients discharged from acute care hospitals [14,15].

Depressive symptoms are highly prevalent among older hospitalized patients [16]. Besides having negative functional and prognostic implications [17], they may increase the risk of iatrogenic events among older in-patients [18]. Additionally, users of anticholinergic medications were recently found to have poorer psychological well-being than non-users [19]. The CRIME study was a valuable opportunity to investigate the potential prognostic interaction between anticholinergic burden and Geriatric Depression Scale (GDS) score. Therefore, we aimed at investigating the role of high GDS score as potential effect modifiers in the association between anticholinergic burden and 1-year mortality in older patients discharged from hospital.

2. Methods

This study uses data from the CRIME to assess Inappropriate Medication use among Elderly complex patients (CRIME) project, a multicenter prospective observational study carried out in seven geriatric and internal medicine acute care wards throughout Italy [20]. Briefly, all patients consecutively admitted to participating wards between June 2010 and May 2011, were asked to participate in the study. Exclusion criteria included age < 65 years and unwillingness to participate in the study. After obtaining a written informed consent, all participants were assessed within the first 24 h from hospital admission and followed until discharge. Information was collected on demographic, socioeconomic, and clinical characteristics, with detailed data collection on pharmacological therapy and comprehensive geriatric assessment. Medications were coded according to the Anatomical Therapeutic and Chemical (ATC) classification [21]. The attending physicians carefully recorded all the drugs taken by the patient before admission, during hospital stay (including date of start and withdrawn), and those prescribed at discharge. Drug name, formulation and daily dosage were recorded for all medications.

After discharge, patients were reassessed at 3, 6, and 12 months. All Ethics Committees at participating institutions approved the study.

Overall, 1123 patients were enrolled in the study. Patients with incomplete baseline data ($N = 3$) and those who died during hospitalization ($N = 39$) were excluded from the present analysis. Patients with incomplete follow-up data ($N = 274$), as well as those for which 15-item Geriatric Depression Scale (GDS) [22] was not applicable because of severely compromised cognitive status ($N = 41$) and those with missing GDS data ($N = 190$) were also excluded, leaving a sample of 576 patients to be included in the analysis.

Patients excluded because of missing GDS data were older (84.5 ± 7.1 vs 79.6 ± 7.0 , $p = .001$), and were more frequently affected by stroke (21.6% vs 9.4%, $p = .001$), dementia (26.8% vs 12.3%, $p = .001$) and BADL dependency (58.9% vs 23.3%, $p = .001$), while the average ACB score was similar among included patients and those excluded because of missing data (1.2 ± 1.2 vs 1.3 ± 1.2 , $p = .158$).

2.1. Outcome

The outcome of the present study was 1-year mortality. Data on living status during follow-up were obtained by interviewing the patients and/or their formal and/or informal caregivers. About patients who died during the follow-up period, date and place of death were retrieved by relatives or caregivers. The municipal registers were consulted when neither patients or relatives or caregivers could be contacted.

2.2. Exposure variables

The ACB score was used to define the exposure to anticholinergic medications [23]. Drugs with possible anticholinergic effects are defined as those with serum anticholinergic activity or in vitro affinity for muscarinic receptors but no known clinically relevant cognitive effects (ACB score 1). Drugs scoring 2 or 3 at ACB scale are those with established, clinically relevant cognitive effects, and definitely considered anticholinergic. The ACB score was chosen for this study because it was externally validated [8,24] and it is considered more accurate in the assessment of central anticholinergic burden [23] compared to other tools mainly focused on peripheral anticholinergic effects [25] or aimed at capturing both central and peripheral effects [26]. ACB score was calculated at discharge.

Depressive symptoms were assessed by 15-item GDS, and patients with GDS score > 5 at discharge were considered affected by depressive symptoms.

The main exposure variable was calculated as follows: ACB score at discharge, a. low (ACB = 0; no ACB medications), b. medium (ACB = 1), and c. high burden (ACB = 2 or more). To investigate the impact of depressive symptoms on the relationship between ACB and prognosis, ACB score at discharge was stratified by the presence or absence of GDS score > 5.

2.3. Covariates

Age, gender, number of diagnoses, history of falls, and number of medications prescribed at discharge were considered as potential confounders in the analysis. Comprehensive geriatric assessment data were collected at the time of discharge. Cognitive impairment was defined as age- and education-adjusted Mini Mental State Examination (MMSE) [27] score < 24. Dependency in at least 1 basic activity of daily living (BADL) was also included in the analysis. Selected diagnoses known to affect prognosis in older populations, including hypertension, heart failure, diabetes, coronary artery disease, atrial fibrillation, peripheral arterial disease, stroke, dementia, chronic obstructive pulmonary disease, and cancer were also considered as potential confounders. Finally, in order to account for continuity of exposure to anticholinergic medications during the first follow-up period after discharge, ACB score at 3-month follow-up was also considered as a potential confounder in the analysis.

2.4. Analytic approach

First, we analyzed the characteristics of patients according to ACB score at discharge among patients with or without high GDS score. Chi-square test was used for categorical variables, and ANOVA one-way for continuous ones. The association between exposure variables and the outcome was explored by Kaplan-Meier curves.

The dose-response relationship between ACB score and mortality was explored in the whole study population by age- and gender-adjusted Cox proportional hazard analysis. Therefore, we built three different Cox proportional hazard models: Model A, adjusted for age and gender; Model B, adjusted for age, gender, cognitive impairment, history of falls, No. of diagnoses, and No. of medications; and Model C, adjusted for age, gender, history of falls, No. of medications, above listed selected diagnoses instead of number of comorbidities and diagnosis of dementia instead of cognitive impairment. Model C was also repeated after further adjusting for ACB score at 3-month follow-up. The interaction term ACB score at discharge*GDS was formally investigated in Cox regression analysis. Such analysis was also repeated by adding variables formerly reported to modify the association between ACB and mortality (i.e. cognitive impairment, history of falls or dependency in BADL) [14,15] to the interaction term.

In order to account for potential residual confounding, sensitivity analyses were carried out by excluding oldest patients (age = 90 or

more), and patients with high comorbidity (no. of diagnoses > 5) or polypharmacy (no. of medications > 5). Attrition bias was investigated by age- and gender-adjusted logistic regression analysis of ACB exposure to loss to follow-up.

Statistical analysis was carried out using SPSS for Win V23.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Overall, GDS score > 5 at discharge was observed in 209 out of 576 patients (36.3%). The average ACB score was 1.3 ± 1.2 among patients with GDS > 5 and 1.0 ± 1.1 among patients with GDS ≤ 5 (p = .077). ACB score categories (0, 1 and 2 or more) were observed in 58 (27.8%), 77 (36.8%) and 74 (35.4%) of patients with depressive symptoms, and in 121 (33.0%), 141 (38.4%) and 105 (28.6%) of patients without depressive symptoms, respectively.

Among patients without depressive symptoms, those with higher ACB score at discharge were older and more frequently affected by heart failure, coronary artery disease, atrial fibrillation and chronic obstructive pulmonary disease compared to patients with ACB = 0. There were fewer women among patients with higher ACB score, while BADL dependency, overall comorbidity and number of prescribed medications were higher (Table 1). Among patients with high GDS score, those with higher ACB score had a greater prevalence of heart failure, coronary artery disease, atrial fibrillation and chronic obstructive pulmonary disease, as well as higher overall comorbidity and number of prescribed medications compared to those with ACB score = 0 (Table 1). ACB medications prescribed at discharge among patients with or without high GDS score are reported in Table 2. The graded reduction of survival observed in relation to ACB score at discharge was more evident among patients with high compared to low GDS score (Fig. 1).

A clear trend for dose-response relationship between ACB score and mortality was observed in the whole study population (Table 3).

The association between ACB score at discharge and mortality in patients with high GDS score was also confirmed after adjusting for potential confounders (Table 4). Age (HR = 1.07, 95%CI = 1.02–1.12) and BADL dependency (HR = 2.15, 95%CI = 1.09–4.26) also qualified as predictor of mortality among depressed patients in Model B, while other predictors of mortality in Model C were age (HR = 1.10,

95%CI = 1.04–1.17), cancer (HR = 5.39, 95%CI = 2.48–11.7), and BADL dependency (HR = 2.88, 95%CI = 1.48–5.63).

The association between ABC score and mortality among patients with high GDS score was stronger in women (HR = 5.31; 95%CI = 1.27–22.1) than in men (HR = 3.05; 95%CI = 0.90–39.2).

The association between ACB score and mortality was weaker among patients with GDS ≤ 5 and it was no longer significant in Model C (HR = 2.32, 95%CI = 0.90–6.24). Predictors of mortality in this group were age (HR = 1.04, 95%CI = 1.01–1.09) and dependency in at least 1 BADL (HR = 2.12, 95%CI = 1.10–4.09) in model B, and cancer (HR = 4.76, 95%CI = 2.45–9.28) and dependency in at least 1 BADL (HR = 2.47, 95%CI = 1.21–5.06) in model C.

When we included ACB score at discharge as a continuous variable in the fully adjusted model C, the association with mortality was confirmed among patients with GDS > 5 (HR = 1.42, 95%CI = 1.10–1.91), but not among those with GDS ≤ 5 (HR = 1.24, 95%CI = 0.95–1.61).

ACB score at 3-month follow-up was similar to that measured at discharge (GDS > 5 1.2 ± 1.3 vs GDS ≤ 5 0.99 ± 1.1, p = .118). The association between ACB score = 2 or more and mortality remained unchanged after further adjusting Model C for ACB score at 3-month follow-up (HR = 3.58; 95%CI = 1.21–10.7) among patients with high GDS score, but not in the GDS ≤ 5 group (HR = 2.44, 95%CI = 0.89–6.13).

The interaction term ACB score at discharge*GDS on mortality in the whole study population was statistically significant (p < .005). However, it was no longer significant when adding history of falls to the interaction term (p = .458), whilst adding cognitive impairment (p = .002) or dependency in at least 1 BADL (p < .001) increased statistical significance of the interaction.

After excluding patients with age = 90 or more, high comorbidity (no. of diagnoses > 5), polypharmacy (no. of medications > 5) or dementia the association between ACB score = 2 or more and mortality among patients with high GDS score was still statistically significant (HR = 3.10, 95%CI = 1.16–11.2, N = 182; HR = 3.57, 95%CI = 1.04–9.02, N = 141; HR = 3.99, 95%CI = 1.03–17.6, N = 122; HR = 3.98, 95%CI = 1.10–15.9, N = 172, respectively).

Finally, no significant association was found between ACB score = 2 or more and dropout rate (N = 274) either in the GDS > 5 (OR = 1.50, 95%CI = 0.86–3.02) or GDS ≤ 5 group (OR = 1.11, 95%CI = 0.61–2.02).

Table 1

Demographic and clinical characteristics of patients stratified by depressive symptoms and ACB score at discharge.

	All patients N = 576	No depressive symptoms (N = 367)			p-value	Depressive symptoms (N = 209)			p-value
		ACB score at discharge				ACB score at discharge			
		0 N = 121	1 N = 141	2 or more N = 105		0 N = 58	1 N = 77	2 or more N = 74	
Age, years	79.6 ± 7.0	76.7 ± 7.1	79.3 ± 6.8	80.1 ± 6.6	0.001	81.0 ± 6.2	81.5 ± 7.3	80.5 ± 7.0	0.679
Gender, F	301 (52.3)	60 (49.6)	51 (36.2)	40 (38.1)	0.067	48 (82.8)	52 (67.5)	50 (67.6)	0.091
Cognitive impairment	247 (42.9)	34 (28.1)	63 (44.7)	41 (39.0)	0.020	29 (50.0)	43 (55.8)	37 (50.0)	0.717
Dependency in at least 1 BADL	134 (23.3)	17 (14.0)	26 (18.4)	28 (26.7)	0.054	16 (27.6)	22 (28.6)	25 (33.8)	0.692
History of falls	160 (27.8)	27 (22.3)	38 (27.0)	23 (21.9)	0.573	16 (27.6)	31 (40.3)	25 (33.8)	0.305
No. of diagnoses	5.3 ± 2.6	4.3 ± 2.5	5.1 ± 2.3	6.2 ± 2.9	0.001	4.5 ± 2.7	5.6 ± 2.5	6.3 ± 2.7	0.001
Hypertension	458 (79.5)	94 (77.7)	121 (85.8)	87 (82.9)	0.225	41 (70.7)	55 (71.4)	60 (81.1)	0.284
Heart failure	163 (28.3)	7 (5.8)	46 (32.6)	50 (47.6)	0.001	4 (6.9)	25 (32.5)	31 (41.9)	0.001
Diabetes	175 (30.4)	37 (30.6)	36 (25.5)	39 (37.1)	0.148	14 (24.1)	25 (32.5)	24 (32.4)	0.503
Coronary artery disease	183 (31.8)	17 (14.0)	41 (29.1)	47 (44.8)	0.001	12 (20.7)	32 (41.6)	34 (45.9)	0.007
Atrial fibrillation	105 (18.2)	10 (8.3)	26 (18.4)	38 (36.2)	0.001	3 (5.2)	12 (15.6)	16 (21.6)	0.030
Peripheral arterial disease	52 (9.0)	7 (5.8)	18 (12.8)	15 (14.3)	0.082	1 (1.7)	9 (11.7)	2 (2.7)	0.018
Stroke	54 (9.4)	13 (10.7)	7 (5.0)	12 (11.4)	0.129	4 (6.9)	8 (10.4)	10 (13.5)	0.469
Dementia	71 (12.3)	11 (9.1)	15 (10.6)	8 (7.6)	0.719	7 (12.1)	17 (22.1)	13 (17.6)	0.320
Chronic obstructive pulmonary disease	228 (39.6)	38 (31.4)	64 (45.4)	51 (48.6)	0.017	15 (25.9)	26 (33.8)	34 (45.9)	0.051
Cancer	84 (14.6)	18 (14.9)	20 (14.2)	20 (19.0)	0.553	7 (12.1)	8 (10.4)	11 (14.9)	0.703
No. of medications	7.7 ± 2.8	5.8 ± 2.4	8.0 ± 2.3	9.4 ± 2.7	0.001	6.0 ± 2.7	7.9 ± 2.6	8.8 ± 2.3	0.001

Data are mean ± SD or number of cases (percentage). P values are from Chi-square or ANOVA one-way test, as appropriate. Cognitive impairment was defined as age- and education-adjusted Mini Mental State Exam score < 24.

Table 2
ACB listed medications prescribed at discharge in the study population.

	Non depressed N = 367	Depressed N = 209
ACB score 1	Furosemide 179 (48.8%), Prednisone 33 (9.0%), Digoxin 28 (7.6%), Methoprolol 25 (6.8%), Isosorbide 21 (5.7%), Atenolol 13 (3.5%), Codeine 11 (3.0%), Warfarin 11 (3.0%), Nifedipine 8 (2.2%), Trazodone 8 (2.2%), Ranitidine 5 (1.4%), Alprazolam 4 (1.1%), Chlortalidone 2 (0.5%), Theophylline 2 (0.5%), Captopril 1 (0.5%), Fentanyl 1 (0.3%), Diazepam 1 (0.3%), Colchicine 1 (0.3%), Hydrocortisone 1 (0.3%), Risperidone 1 (0.3)	Furosemide 110 (52.6%), Prednisone 17 (8.1%), Methoprolol 16 (7.7%), Codeine 14 (6.7%), Digoxin 13 (6.2%), Isosorbide 12 (5.7%), Alprazolam 11 (5.3%), Warfarin 8 (3.8%), Ranitidine 7 (3.3%), Nifedipine 5 (2.4%), Atenolol 4 (1.9%), Trazodone 4 (1.9%), Fentanyl 3 (1.4%), Diazepam 2 (1.0%), Chlortalidone 1 (0.5%), Theophylline 1 (0.5%), Captopril 1 (0.5%)
ACB score 2	Carbamazepine 5 (1.4%), Oxcarbazepine 1 (0.3%), Meperidine 1 (0.3%)	Carbamazepine 1 (0.5%)
ACB score 3	Quetiapine 6 (1.6%), Paroxetine 3 (0.8%), Promazine 2 (0.5%), Amitriptiline 1 (0.3%), Scopolamine 1 (0.3%), Oxybutinine 1 (0.3%), Orphenadrine 1 (0.3%)	Quetiapine 6 (2.9%), Paroxetine 3 (1.4%), Promazine 1 (0.5%), Olanzapine 1 (0.5%), Amitriptiline 1 (0.5%), Scopolamine 1 (0.5%)

Data are number (percentage).

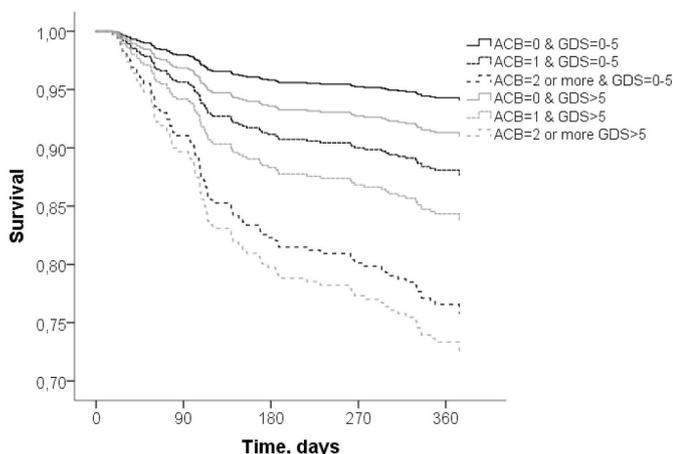


Fig. 1. The Kaplan-Meier curves showing survival associated with ACB anticholinergic burden and depressive symptoms.

Table 3
Cox regression analysis exploring dose-response relationship between ACB score and mortality in the whole study population.

ACB score	Mortality rate ^a	HR (95%CI)
0	12 (6.7)	1.0
1	29 (13.3)	1.70 (0.86–3.63)
2	27 (25.5)	3.32 (1.67–6.60)
3	11 (23.9)	3.31 (1.45–7.56)
4	5 (26.3)	4.16 (1.46–11.5)
5	2 (25.0)	6.38 (1.41–28.9)

^a Data are number of cases (percentage).

Table 4
Cox proportional hazard models of the relationship between ACB score at discharge and 1-year mortality stratified by the depressive symptoms.

	Mortality rate (%)	Model A	Model B	Model C
ACB score at discharge				
No depressive symptoms (N = 367)				
0	7 (5.8)	1.0	1.0	1.0
1	17 (12.1)	1.77 (0.73–4.29)	1.58 (0.64–3.91)	1.65 (0.65–4.70)
2 or more	25 (23.8)	3.63 (1.56–8.44)	2.74 (1.10–6.90)	2.32 (0.90–6.24)
Depressive symptoms (N = 209)				
0	5 (8.6)	1.0	1.0	1.0
1	12 (15.6)	1.62 (0.56–4.70)	1.55 (0.60–4.37)	1.52 (0.50–4.80)
2 or more	20 (27.0)	3.35 (1.20–8.75)	3.19 (1.20–9.06)	3.70 (1.18–11.6)

Model A, adjusted for age and gender; Model B, adjusted for age, gender, cognitive impairment, history of falls, No. of diagnoses, and No. of medications; Model C, as for model B with Hypertension, Heart failure, Diabetes, Coronary artery disease, Atrial fibrillation, Peripheral arterial disease, Stroke, Chronic obstructive pulmonary disease, and Cancer instead of No. of diagnoses and diagnosis of Dementia instead of cognitive impairment.

4. Discussion

Our study confirms that anticholinergic burden measured by ACB score may be associated with excessive mortality risk among depressed older patients discharged from acute care hospital, thus suggesting that high GDS score may represent a relevant effect modifier in the association between anticholinergic burden and mortality.

Anticholinergic medications are known to be responsible for central and peripheral adverse effects [28]. Mechanisms potentially involved in the association between the use of these drugs and prognosis may include cardiovascular (eg, arrhythmias, syncope, ischemia) and neurologic (eg, hallucinations, confusion, seizure) adverse events [29]. Additionally, age-related changes in pharmacokinetics and pharmacodynamics, as well as increased permeability of blood-brain barriers may further worsen cholinergic neurotransmission already impaired by age-related acetylcholine depletion, thus predisposing older patients to increased risk of adverse effects from anticholinergic drugs [30,31]. Non-neuronal cholinergic system is present on immunocompetent cells at the site of inflammation [32], and the stimulation of nicotinic receptors may inhibit adaptive and innate immune response [33]. Thus, anticholinergic medications may also counteract these immune-modulatory effects leading to inflammation and possible negative impact on survival.

Anticholinergic medications were also found having negative effects on mood [34], and depressive symptoms themselves have negative prognostic implications in older populations [35,36]. The finding of an increased risk of mortality among patients with either high ACB score and high GDS score suggests that impaired mood may increase vulnerability to negative prognostic effects of anticholinergic medications and/or depressive symptoms may represent a mediator of their negative prognostic effects.

Potential reasons explaining the impact of high GDS score on the observed associations may be related to neurobiological mechanisms involved in the development of depression. Evidence from experimental studies suggests that an imbalance of multiple neurobiological systems

underlying depression may lead to cholinergic dysfunction of hippocampus, amygdala and pre-frontal cortex which, in turn, may predispose and/or precipitate cognitive and depressive disorder [37]. Thus, increased anticholinergic burden may further disrupt cholinergic neurotransmission already impaired in selected brain areas. Patients carrying high GDS score may also have high susceptibility to negative iatrogenic events. Indeed, GDS score > 5 was found associated with increased risk of adverse drug reactions in a large population of older hospitalized patients [18]. Furthermore, anticholinergic medications may worsen physical performance, muscle strength, and BADL dependency [38], and depressive symptoms are highly prevalent among disabled older patients [16]. Additionally, ACB score was found associated with impaired gait-balance and consequent recurrent or injurious falls [39], and falls, in turn, may be associated with depressive symptoms [40].

Our findings suggest that hospital physicians should be aware of the excessive mortality risk associated to the prescription of anticholinergic medications at discharge of older people with high GDS score. Hospitalization should always be considered as a clue to identify pre-existing or new onset depressive symptoms and to verify the possibility to switch to or start drugs with no or less anticholinergic burden whenever possible (e.g. avoiding tricyclics, trazodone or paroxetine). The persistence of clinical indications to prescribe anticholinergic drugs should also be carefully scrutinized, and eventually a slow and gradual withdrawal being carefully monitored during post-acute care should be started when indications are no longer present.

Our study has several limitations. Given the observational design, confounding by indication is a relevant limitation in our study. Even if results were confirmed in sensitivity analyses and attrition bias seems to be not relevant, a greater overall comorbidity and number of medications, as well as higher prevalence of selected diagnoses, cognitive and functional impairment were observed among patients with high baseline anticholinergic burden. Additionally, our results identify variables that by themselves may influence the outcome, and we could not account for illness severity, duration and management of individual diagnoses, and life expectancy. Furthermore, we only used the ACB score to assess exposure to anticholinergic burden, so we cannot rule out that other measures of anticholinergic burden may have yielded different results. However, ACB scale was formerly validated in regards to its predictivity of cognitive outcomes, physical functioning and mortality [41]. Similarly, GDS scale was the only measure used for the assessment of mood status. The short duration of follow-up does not allow to optimally explore the association between ACB and prognosis. Additionally, we could only partly account for duration of exposure to anticholinergic medications because data about medications were not available over 3-month follow-up.

Furthermore, our results may lack in precision of estimates due to the small sample size. The wide confidence intervals observed may reflect the low number of events, and the finding of a not significant trend for association between ACB score and mortality among patients with GDS ≤ 5 in the fully adjusted model does not mean that anticholinergic medications can be considered safe in these patients. The small sample size also limits the possibility to draw definitive conclusions about data obtained by gender stratification, and did not allow to explore dose-response relationship between ACB score and mortality after stratification by GDS score. Finally, our results apply to a population of older patients discharged from acute care hospitals and cannot be generalized to the general older population. Nevertheless, the strengths of our study are mainly represented by the inclusion of an unselected population of older hospitalized patients, the detailed assessment of medications, and the use of comprehensive geriatric assessment which allowed to stratify the analysis by high GDS score and to explore the independent effect of ACB score after adjusting for a wide set of potential confounders, including other potential mediators such as history of falls, cognitive impairment and BADL dependency.

In conclusion, ACB score at discharge may predict mortality among

older patients discharged from acute care hospital carrying a high GDS score. Hospital physician should be aware that prescribing anticholinergic medications in such a vulnerable population may have negative prognostic implications. Thus, hospitalization should be considered a clue to identify patients carrying high GDS score in the hospital setting and to revise overall pharmacological treatment to reduce the anticholinergic burden at discharge whenever possible.

Competing interests

All Authors declare to have no competing interests with this manuscript.

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Authors' contributions

Andrea Corsonello, Annalisa Cozza, Mirko Di Rosa and Paolo Fabbietti participated in data analysis, manuscript writing and revising, and manuscript approval.

Sonia D'Alia contributed in data analysis and revising the manuscript for important intellectual content and approval.

Graziano Onder, Stefano Volpato, Carmelinda Ruggiero, Antonio Cherubini and Andrea Corsonello participated in data collection and writing, revising and approving manuscript.

Fabrizia Lattanzio participated in writing the manuscript, revising it for important intellectual content, and approval.

Declarations of interest

None.

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The complete list of CRIME study investigators was previously published [20].

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