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Association of anticholinergic drug use with postoperative mortality among patients with hip fracture. A nationwide cohort study

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ABSTRACT

Purpose: Anticholinergic (AC) drugs are associated with various determinantal outcomes. Data regarding the effect of AC drugs on mortality among geriatric hip fracture patients are limited and inconsistent.
Methods: Using Danish health registries, we identified 31,443 patients aged ≥65 years undergoing hip fracture surgery. AC burden was assessed 90 days before surgery by the Anticholinergic Cognitive Burden (ACB) score and number of AC drugs. Logistic and Cox regression producing odds ratios (OR) and hazard ratios (HR) for 30- and 365- day mortality, adjusting for age, sex, and comorbidities were computed.
Results: AC drugs were redeemed by 42% of patients. The 30-day mortality increased from 7% for patients with ACB score of 0 to 16% for patients with ACB score of ≥5, corresponding to an adjusted OR 2.5 (CI: 2.0–3.1). The equivalent adjusted HR for 365-mortality was 1.9 (CI: 1.6–2.1). Using count of AC drugs as exposure we found a stepwise increase in ORs and HRs with increased number of AC drugs; Compared to non-users, adjusted ORs for 30-days mortality were 1.6 (CI: 1.4–1.7), 1.9 (CI: 1.7–2.1), and 2.3 (CI: 1.9–2.7) for users of 1, 2 and 3+ AC drugs. HRs for 365-day mortality were 1.4 (CI: 1.3–1.5), 1.6 (CI: 1.5–1.7) and 1.8 (CI: 1.7–2.0).
Conclusion: Use of AC drugs was associated with increased 30-day and 365-day mortality among older adults with hip fracture. Simply counting the number of AC drugs may be a clinically relevant and easy AC risk assessment tool. Continued effort to reduce AC drug-use is relevant.

1. Introduction

Up to 50% of the older population are routinely exposed to drugs with anticholinergic (AC) properties (Salahudeen et al., 2015). AC drugs are used on many indications to treat prevalent disorders, including urinary dysfunction, airway diseases, gastrointestinal conditions, and psychiatric disorders. They act as competitive antagonists to acetylcholine, inhibiting the activity of muscarinic receptors in both the central and peripheral nervous system, which can cause adverse effects such as constipation, blurred vision, sedation, trouble urinating, drowsiness, and cognitive impairment (Yayla et al., 2015; Mintzer & Burns, 2000). Concomitant prescribing of multiple drugs with AC properties increases the AC burden and therefore the amount and severity of AC side effects. Depending on the study design and AC quantification method (Lisibach et al., 2020; Mangoni et al., 2013), some, but not all studies reported an association between the use of AC drugs and mortality among older adults (Salahudeen et al., 2015; Lisibach et al., 2020; Ali et al., 2020). A clear association has been reported among community-dwelling older adults (Sarbacker et al., 2017; Lu et al., 2015) whereas the association among hospitalized older adults remains disputable (Ali et al., 2020; Lattanzio et al., 2018; Sørensen et al., 2021).

Hip fracture is a common cause of hospitalization and death among the older population (Katsoulis et al., 2017). Preexisting multimorbidity, polypharmacy and high age all contribute to a high complication rate and a poor prognosis (Katsoulis et al., 2017; Haentjens et al., 2010; Xu et al., 2019). Patients with hip fracture are often frail and more susceptible to adverse effects of a wide range of medications, including AC drugs (Yayla et al., 2015; Mintzer & Burns, 2000; Mangoni et al., 2013; Hershkovitz et al., 2018; Björkelund et al., 2010) and an increased AC burden have been reported to be associated with impaired cognitive

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(Mangoni et al., 2013) and physical function (Hershkovitz et al., 2018) and delirium (Björkelund et al., 2010) . This is partly explained by compromised blood vessel autoregulation (Marzoughi et al., 2021) and decreased physical reserves in older surgical patients (Haentjens et al., 2010; Hamner et al., 2012; Grüne & Klimek, 2017). In addition, augmented permeability of the blood-brain barrier, impaired metabolism, and renal clearance (Collamati et al., 2016) may be explanations for increased adverse events among older patients.

Only few studies have investigated the effect of AC drugs on mortality among hip fracture patients (Mangoni et al., 2013; Panula et al., 2009; Ablett et al., 2019), two of which are based on hip fracture patients aged 65 years and above (Mangoni et al., 2013; Panula et al., 2009). The existing studies are limited by small sample sizes (71 and 461 patients), cross-sectional study design, and lack of adjustment for relevant confounders, which may explain the inconsistent results.

Various summarized point scales for quantification of all AC drugs given to a patient have been developed (Boustani et al., 2008; Lisibach et al., 2021). No consensus on a standardized measure of AC burden exists and the complexity of most AC scoring systems may serve as an obstacle for practical applicability. We therefore conducted a population-based cohort study to examine the prevalence of AC drug use among hip fracture patients aged 65 years and above and to examine the association between AC drug use and mortality within 30- and 365 days following hip fracture surgery assessing the AC burden with the cumulative Anticholinergic Cognitive Burden (ACB) score (Boustani et al., 2008; The 2012 ACB List, 2023) and a simple count of the number of AC drugs.

2. Methods

This study is based on data from the Danish Health care registries. Utilization of health care services is free of charge for all residents in Denmark (approximately 5.8mio. citizens in 2021) due to a tax-supported health care system covering the use of general practitioners, public hospitals and partial reimbursements of prescription medicine (Schmidt et al., 2019).

2.1. Data sources

Complete and valid data linkage of all Danish registries on an individual level is possible due to the unique and ubiquitously used 10-digit civil personal registration number assigned to each Danish Citizen at birth or upon immigration (Schmidt et al., 2019).

- The DMHFR is a clinical quality database holding surgery- and patient related information on all patients aged ≥65 years undergoing hip fracture surgery in Denmark. Patients are included if the following criteria are fulfilled: 1) A primary diagnosis of hip fracture (DS720 - DS722), 2) A sub-code indicating the side of the fracture, 3) A surgical procedure code corresponding to a hip fracture operation. Reporting to the database has been mandatory by law since 2006 (Kristensen et al., 2020).
- The Danish National Patient Registry has registered all somatic hospital admission since 1977 and all hospital outpatient and emergency visits since 1995. Diagnoses are coded according to International Classification of Diseases 10th edition (ICD-10) since 1994 (Schmidt et al., 2015).
- The Danish Civil Registration System (CRS) provides information on migration- and vital status allowing for long-term and complete follow-up for all individuals. The CRS is updated daily (Schmidt et al., 2014).
- The Danish National Prescription Registry includes information on all reimbursed prescriptions dispensed from community pharmacies nationwide since 2003 (Kildemoes et al., 2011).

2.2. Study population

Patients aged 65 years and above undergoing surgery for an incident hip fracture from January 1, 2014, to December 31, 2018, were identified in the DMHFR (n = 31,443).

2.3. Definition of anticholinergic exposure

Information on AC dispensing in the period 90 days prior to hip fracture surgery was collected from the National Prescription Registry. This period was chosen to identify current users of AC medications as most drugs are dispensed for 3 months at a time.

AC drug use was assessed in two ways:

1) Calculation of the ACB score was based on the 2012 version of the ACB score (The 2012 ACB List, 2023) where a modified list, adapted to the Danish market, with corresponding scores of each drug was made (Appendix Table A.1). This ACB scoring system has been widely examined and validated as a predictor of mortality (Salahudeen et al., 2015; Lisibach et al., 2020; Ali et al., 2020). This employs a three-point scale according to each drugs' AC activity. A score of one is given drugs with serum AC activity or in vitro affinity to muscarinic receptors, whereas drugs with a score of two and three exert moderate to strong clinical cognitive AC effects. For each drug type dispensed to the patient within the 90 days prior to index date, points were assigned according to the list and a summarized score was computed, representing the total AC burden (Boustani et al., 2008; Campbell et al., 2012). We categorized the patients into four groups: ACB=0, ACB=1–2, ACB=3–4 and ACB≥5.
2) Counting the number of AC drugs used. This method was included to evaluate a more easily implementable method. The patients were categorized into four groups with a total of 0, 1, 2 and 3+ numbers of AC drugs.

2.4. Follow-up and study outcome

In all analyses, the date of the primary hip fracture repair surgery was set as the index date marking start of follow up. Patients were followed until the date of death, which is the study outcome, emigration, until one year of follow-up, or 1st of January 2019, whichever came first. Information on death and emigration was retrieved from the CRS (Schmidt et al., 2014). Mortality analyses included all-cause mortality during the first 365-days, also including peri-operative and in-hospital deaths.

2.5. Patient characteristics

Comorbidities diagnosed before index hospitalization for hip fracture in a 10-year look back period were collected from the Danish National Patient Registry. Diagnoses were summarized using the Charlson Comorbidity Index (CCI) score for each patient. The CCI includes 19 major disease categories and the corresponding diagnosis codes are registered at in- and outpatient visits to Danish public hospitals according to the ICD-10 (Charlson et al., 1987; Madsen et al., 2015). The CCI score was used as a continuous variable when used for confounder adjustment and in a categorized form (0, 1, 2, or 3+ points corresponding to no-, mild-, moderate-, or severe comorbidity) for the stratified analysis.

From the DMHFR we retrieved data on additional potential confounders at the day of surgery including year of surgery, type of residence, hip fracture type and Body Mass Index (BMI). Data on age and sex was retrieved from the patient civil personal registration number.

2.6. Statistical analysis

Patient characteristics were described as counts and proportions, for

the overall study population and according to the categories of AC drug use according to the ACB scores and count of drugs.

We calculated the proportion of patients who died within the first postoperative year divided by the total number of patients in the respective exposure group. We estimated crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) for 30-days mortality for ACB score groups and AC count groups by logistic regression. We plotted the Kaplan-Meier curves for mortality for each ACB score-group. Furthermore, we estimated the crude and adjusted hazard ratios (HR) and 95% CI for one year mortality by a Cox proportional hazards regression for each ACB score-group and each ACB-count group.

All analyses are reported as crude estimates and adjusted for age (represented as a second-grade polynomial), sex and comorbidities (continuous variable) as defined by CCI score. Additionally, analyses were stratified by age- sex- and CCI score. The proportional hazards assumption of the Cox analyses was checked using log-log curves and found to hold.

Reporting of this study follows the STROBE guidelines (von Elm et al., 2014).

Statistical analyses were carried out using SAS statistical software (SAS Institute Inc., Cary, USA)) and R v.3.5.1 (R Foundation for Statistical Computing).

3. Results

3.1. Participants and baseline characteristics

Table 1 provides baseline characteristics at time of admission according to the patients' ACB score. The median age of our study population was 83 years and 31% were males.

Of the 31,443 patients, 42% were prescribed AC medications in the 90 days prior to hip fracture surgery and 30% (9536) of these had an ACB score = 1–2, 9% (2902) a score of 3–4 and 2% (674) had an ACB score ≥5.

Patients were generally younger the higher the ACB score. A higher prevalence of comorbidity was observed, and a higher prevalence resided in nursing homes among patients with ACB score ≥5 compared to all lower ACB categories. Information on BMI was missing for nearly 19% the participants, yet this did not differ across ACB subgroups. Baseline characteristics among the groups with increasing AC count was distributed correspondingly (Table 2). An overview of the most commonly prescribed drugs on the ACB list is shown in Appendix Table A.2. Listed among the 15 most prevalent prescribed drugs are, among others, strong analgesics, and neuroleptics.

3.2. Association between AC drug use and mortality

The proportions of patients who died within 30 days were 7%, 14%, 12%, 16% for patients with ACB score of 0, 1–2, 3–4, and ≥5 and the proportions of patients who died within 365 days were 21%, 35%, 31% and 36% for patients with ACB score of 0, 1–2, 3–4. The Kaplan-Meier curves in Fig. 1 illustrate 365-day mortality by the cumulative ACB score groups.

Compared to patients with ACB=0, the adjusted ORs for 30-day mortality were 1.7 (CI: 1.6–1.9), 1.6 (CI: 1.4–1.8) and 2.5 (CI: 2.0–3.1) for patients with ACB=1–2, ACB=3–4, and ACB≥5, respectively. The corresponding adjusted HRs for 365-day mortality were 1.5 (CI: 1.4–1.5), 1.5 (CI: 1.4–1.6) and 1.9 (CI: 1.6–2.1)(Fig. 2).

The Kaplan-Meier curves in Fig. 3 indicates a lower mortality among patients not taking any AC drugs and a clear stepwise increase in mortality with use of higher numbers of AC drugs was observed.

The relative estimates show a similar pattern and are shown in Fig. 4; mortality risk 30- and 365-days postoperatively, ORs, and HRs with corresponding 95% CIs of the four groups, categorized by number of AC drugs. Within 30 days, 7%, 13%, 15% and 18% of patients taking 0, 1, 2, and 3+ AC drugs had died. Corresponding numbers for 365-day mortality were 21%, 32%, 38% and 42%.

Compared to non-users of AC drugs, ORs for 30-day mortality were 1.6 (CI: 1.4–1.7), 1.9 (CI: 1.7–2.1) and 2.3 (CI: 1.9–2.7) for users of 1, 2 and 3+ AC drugs at the time of hip fracture. The respective adjusted HRs for 365-day mortality were 1.4 (CI: 1.3–1.5), 1.6 (CI: 1.5–1.7), and 1.8 (CI: 1.7–2.0).

Table 1
Demographic data on the study population categorized by ACB score.

	All patients	ACB score			
	N (%)	0 N (%)	1–2 N (%)	3–4 N (%)	5 + N (%)
All	31,443 (100)	18,331 (58.3)	9536 (30.3)	2902 (9.2)	674 (2.1)
Age category					
65 - 75	6715 (21.4)	4264 (23.3)	1610 (16.9)	647 (22.3)	194 (28.8)
75 - 85	11,426 (36.3)	6729 (36.7)	3313 (34.7)	1123 (38.7)	261 (38.7)
85+	13,302 (42.3)	7338 (40.0)	4613 (48.4)	1132 (39.0)	219 (32.5)
Sex					
Male	9630 (30.6)	5513 (30.1)	2998 (31.4)	914 (31.5)	205 (30.4)
Female	21,813 (69.4)	12,818 (69.9)	6538 (68.6)	1988 (68.5)	469 (69.6)
BMI category					
10–19.9	4083 (13.0)	2415 (13.2)	1221 (12.8)	359 (12.4)	88 (13.1)
20 - 24.9	12,450 (39.6)	7521 (41.0)	3561 (37.3)	1150 (39.6)	218 (32.3)
25 - 29.9	6866 (21.8)	3950 (21.5)	2125 (22.3)	628 (21.6)	163 (24.2)
30 - 51	2133 (6.8)	1020 (5.6)	826 (8.7)	209 (7.2)	78 (11.6)
Missing data	5911 (18.8)	3425 (18.7)	1803 (18.9)	556 (19.2)	127 (18.8)
CCI-score					
0	11,862 (37.7)	8349 (45.5)	2526 (26.5)	826 (28.5)	161 (23.9)
1	7301 (23.2)	4103 (22.4)	2305 (24.2)	749 (25.8)	144 (21.4)
2	5653 (18.0)	3074 (16.8)	1894 (19.9)	548 (18.9)	137 (20.3)
3+	6627 (21.1)	2805 (15.3)	2811 (29.5)	779 (26.8)	232 (34.4)
Year of surgery					
2014	6682 (21.3)	3730 ()	2153 ()	634 ()	165 ()
2015	6570 (20.9)	3753 (20.9)	2036 (20.6)	643 (21.9)	138 (21.6)
2016	6502 (20.7)	3787 (20.7)	1988 (20.6)	575 (20.6)	152 (21.9)
2017	6380 (20.3)	3783 (20.3)	1899 (20.6)	580 (19.4)	118 (20.9)
2018	5309 (16.9)	3278 (16.9)	1460 (17.2)	470 (15.9)	101 (16.5)
Residence					
Own home	21,864 (69.5)	13,598 (74.2)	6198 (65.0)	1698 (58.5)	370 (54.9)
Nursing home	6796 (21.6)	3179 (17.3)	2428 (25.5)	946 (32.6)	243 (36.1)
Missing data	2783 (8.9)	1554 (8.5)	910 (9.5)	258 (8.9)	61 (9.1)
Fracture type					
Non-displaced medial	1823 (5.8)	1142 (6.2)	475 (5.0)	176 (6.1)	30 (4.5)
Medial displaced	11,588 (36.9)	6647 (36.3)	3550 (37.2)	1134 (39.1)	257 (38.1)
Pertrochanteric/ subtrochanteric	14,349 (45.6)	8362 (45.6)	4405 (46.2)	1262 (43.5)	320 (47.5)
Missing data	3683 (11.7)	2180 (11.9)	1106 (11.6)	330 (11.4)	67 (9.9)

ACB: Anticholinergic Cognitive Burden, BMI: Body Mass Index, CCI: Charlson Comorbidity Index.

Table 2
Demographic data on the study population categorized by number of anticholinergic drugs.

	All patients	Number of anticholinergic drugs			
		0	1	2	3 +
	N (%)	N (%)	N (%)	N (%)	N (%)
All	31,443	18,331	8529	3332	1251
	(100)	(58.3)	(27.1)	(10.6)	(4.0)
Age category					
65 - 75	6715	4264	1600	583	268
	(21.4)	(23.3)	(18.8)	(17.5)	(21.4)
75 - 85	11,426	6729	3023	1214	460
	(36.3)	(36.7)	(35.4)	(36.4)	(36.8)
85+	13,302	7338	3906	1535	523
	(42.3)	(40.0)	(45.8)	(46.1)	(41.8)
Sex					
Male	9630	5513	2700	1017	400
	(30.6)	(30.1)	(31.7)	(30.5)	(32.0)
Female	21,813	12,818	5829	2315	851
	(69.4)	(69.9)	(68.3)	(69.5)	(68.0)
BMI category					
10–19.9	4083	2415	1053	423	192
	(13.0)	(13.2)	(12.3)	(12.7)	(15.3)
20 - 24.9	12,450	7521	3278	1201	450
	(39.6)	(41.0)	(38.4)	(36.0)	(36.0)
25 - 29.9	6866	3950	1877	762	277
	(21.8)	(21.5)	(22.0)	(22.9)	(22.1)
30 - 51	2133	1020	691	299	123
	(6.8)	(5.6)	(8.1)	(9.0)	(9.8)
Missing data	5911	3425	1630	647	209
	(18.8)	(18.7)	(19.1)	(19.4)	(16.7)
CCI-score					
0	11,862	8349	2547	746	220
	(37.7)	(45.5)	(29.9)	(22.4)	(17.6)
1	7301	4103	2116	821	261
	(23.2)	(22.4)	(24.8)	(24.6)	(20.9)
2	5653	3074	1629	682	268
	(18.0)	(16.8)	(19.1)	(20.5)	(21.4)
3+	6627	2805	2237	1083	502
	(21.1)	(15.3)	(26.2)	(32.5)	(40.1)
Year of surgery					
2014	6682	3730	1874	760	318
	(21.3)	(20.3)	(22.0)	(22.8)	(25.5)
2015	6570	3753	1836	710	271
	(20.9)	(20.5)	(21.5)	(21.3)	(21.2)
2016	6502	3787	1753	704	258
	(20.7)	(20.6)	(20.6)	(21.1)	(20.6)
2017	6380	3783	1724	651	222
	(20.3)	(20.6)	(20.2)	(19.5)	(17.8)
2018	5309	3278	1342	507	182
	(16.9)	(17.9)	(15.7)	(15.2)	(14.5)
Residence					
Own home	21,864	13,598	5485	2046	735
	(69.5)	(74.2)	(64.3)	(61.4)	(58.8)
Nursing home	6796	3179	2237	974	406
	(21.6)	(17.3)	(26.2)	(29.2)	(32.5)
Missing data	2783	1554	807	312	110
	(8.9)	(8.5)	(9.5)	(9.4)	(8.8)
Fracture type					
Non-displaced medial	1823	1142	432	183	66
	(5.8)	(6.2)	(5.1)	(5.5)	(5.3)
Medial displaced	11,588	6647	3210	1249	482
	(36.9)	(36.3)	(37.6)	(37.5)	(38.5)
Pertrochanteric/ subtrochanteric	14,349	8362	3879	1523	585
	(45.6)	(45.6)	(45.5)	(45.7)	(46.8)
Missing data	3683	2180	1008	377	118
	(11.7)	(11.9)	(11.8)	(11.3)	(9.4)

ACB: Anticholinergic Cognitive Burden, BMI: Body Mass Index, CCI: Charlson Comorbidity Index.

3.3. Stratified analyses

In general, when analyses were stratified by age, gender and CCI score, similar results were found with both increased adjusted ORs and HRs of 30- and 365-day mortality for both increasing ACB scores and higher number of AC-drugs (Appendix Table A.3, A.4, A.5, and A.6). Corresponding to the preceding analyses, an association between higher number of AC drugs and mortality was observed (Appendix A.5 and A.6).

4. Discussion

In this large-scale cohort study, we found that use of AC drugs within three months prior to hip fracture surgery was associated with increased 30- and 365-day all-cause mortality. Patients with higher AC burden according to the ACB score had 1.6- to 2.5-fold higher odds of 30-day mortality and 1.5 to 1.9-fold increased hazard of death in the first postoperative year compared with those not taking AC drugs. No clear relationship between increasing ACB score and mortality was observed. In contrast, an increasing *number* of AC-drugs showed an association with increased mortality, and patients taking more than 3 AC drugs had 2.3-fold increased 30-day mortality and 1.8-fold increased 365-day mortality compared with non-users.

4.1. Comparison with previous literature

Direct comparison with other studies remains impeded due to methodological disparities (Mangoni et al., 2013; Panula et al., 2009).

Panula et al. demonstrated a significant excess postoperative mortality for men exclusively (Panula et al., 2009). In contrast to our study no AC burden scales were applied, and exposure was defined dichotomously comparing users of any AC drugs to non-users. Mangoni et al. (Mangoni et al., 2013) showed increased mortality only when applying some of the AC burden scales but neither ACB score nor total number of AC drugs. Both previous studies were underpowered, which could serve as an obstacle for recognition of association due to type 2 error (Mangoni et al., 2013; Panula et al., 2009). This barrier was addressed in our study by inclusion of a substantially larger sample size and contrary to previous studies we found both AC quantification methods to be associated with increased mortality.

Multiple predictors of postoperative mortality following a hip fracture have been identified (Xu et al., 2019), yet sparse literature exist on the relation of inappropriate pharmacotherapy and mortality (Harstedt et al., 2016). Adverse effects of AC drugs can be enhanced not only through additive AC-AC drug interactions. Interactions between AC drugs and non-AC-drugs and common chronic diseases in the older population affecting AC transmission, such as dementia and tachyarrhythmias, could potentially increase mortality risk (Miller, 2002). The complexity of pharmacotherapy increases with multimorbidity and central cholinergic transmission decline with age. This increases the susceptibility to AC blocking of acetylcholine on muscarinic receptors located in the peripheral and central nervous system (Collamati et al., 2016; Tune, 2001). Additionally, AC drugs can have increased toxicity in the aging brain due to augmented permeability of the blood-brain barrier, impaired metabolism, and renal clearance (Collamati et al., 2016). Old and frail patients undergoing emergency surgery represent a particularly vulnerable population considering their reduced physical reserves and compromised autoregulation (Haentjens et al., 2010; Hamner et al., 2012; Grüne & Klimek, 2017), possibly amplifying the negative effects of AC drugs. Various links between AC drug exposure and mortality have been suggested previously and include some of the most common causes of deaths following hip fracture, such as pneumonia, cardiovascular disease, and stroke (von Friesendorff et al., 2016; Tan et al., 2018; Myint et al., 2015; Chatterjee et al., 2016). Our analyses demonstrated a similar strength of association between AC exposure and mortality among all the age groups, suggesting a need for caution in prescribing AC drugs for all patients over 65 years.

4.2. Methodological considerations

To our knowledge, this study is the first large nationwide cohort,

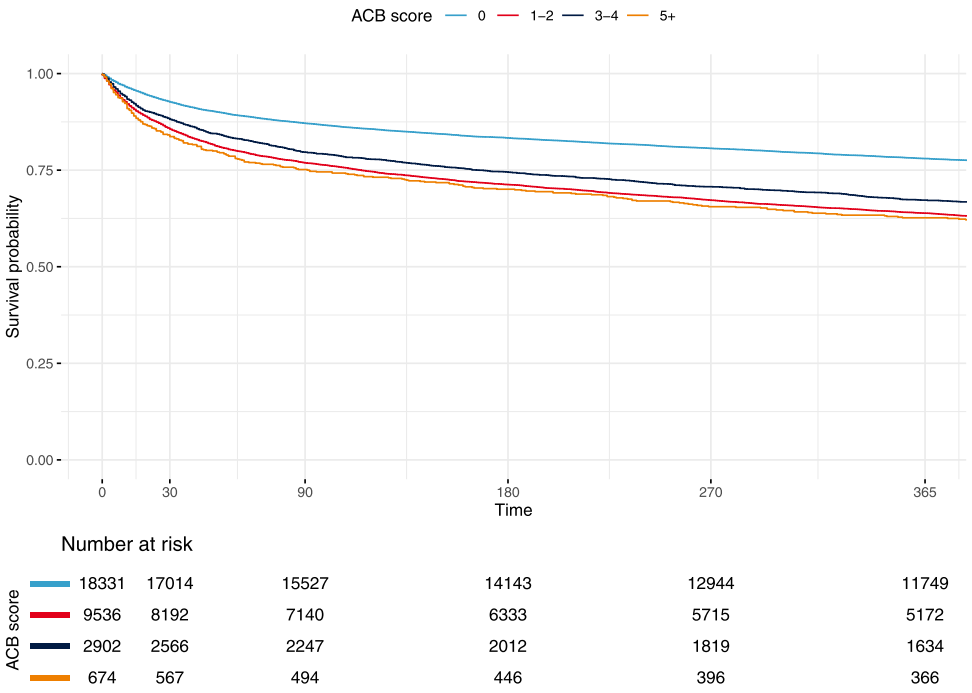

Fig. 1. Kaplan-Meier curves on 365-day mortality according to Anticholinergic Cognitive Burden (ACB) groups.

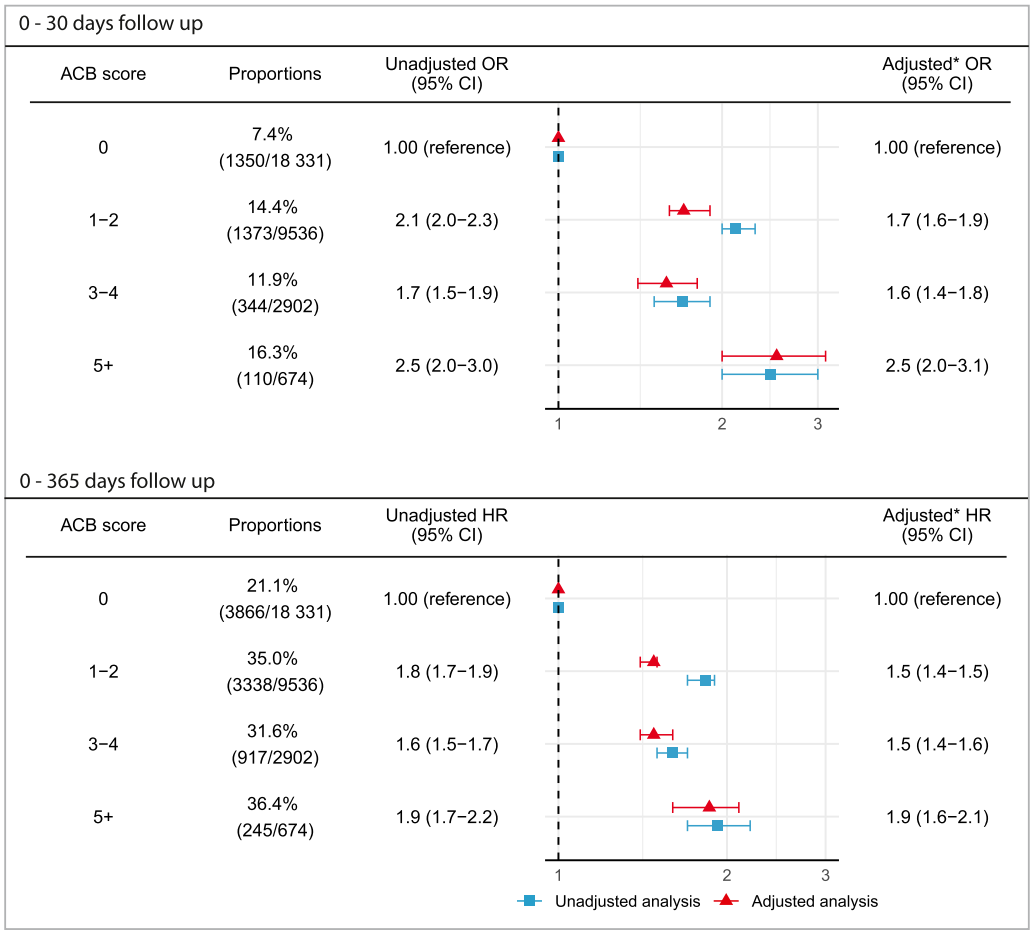

Fig. 2. Unadjusted and adjusted logistic regression analysis for anticholinergic burden and 30-day mortality and unadjusted and adjusted cox regression analysis for anticholinergic burden and 365-day mortality
* Adjusted for age, sex and Charlsons Comorbidity Index score
ACB: Anticholinergic Cognitive Burden
CI: Confidence interval
HR: Hazard Ratio
OR: Odds ratio.

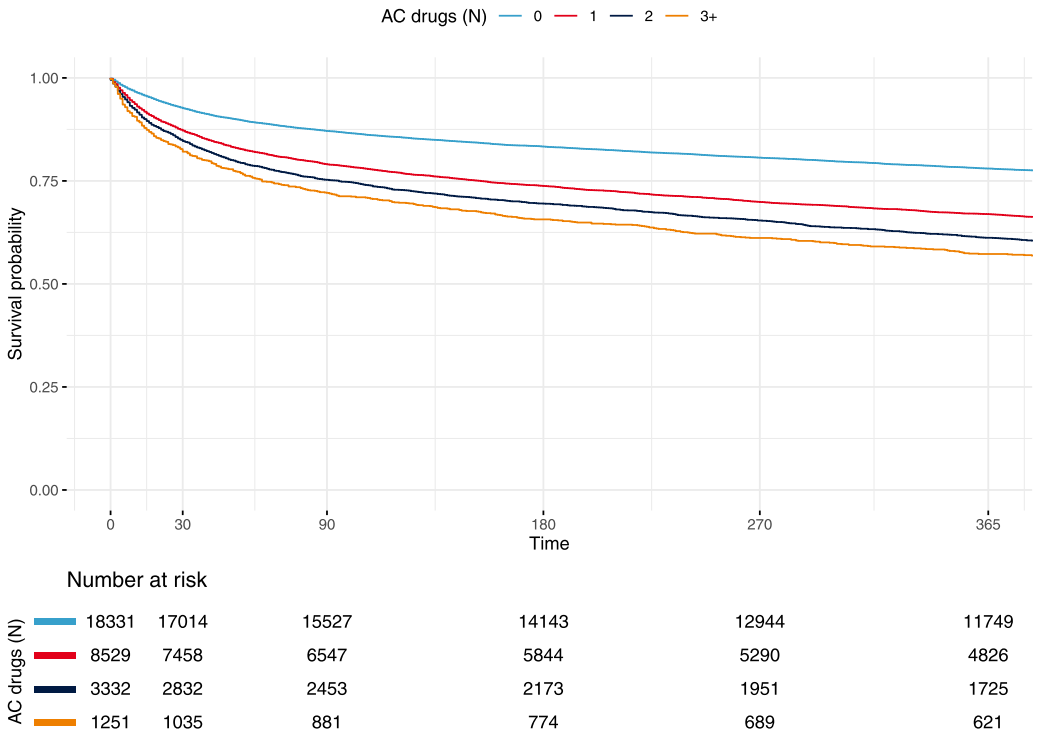

Fig. 3. Kaplan-Meier curves on 365-day mortality according to number of anticholinergic (AC) drugs.

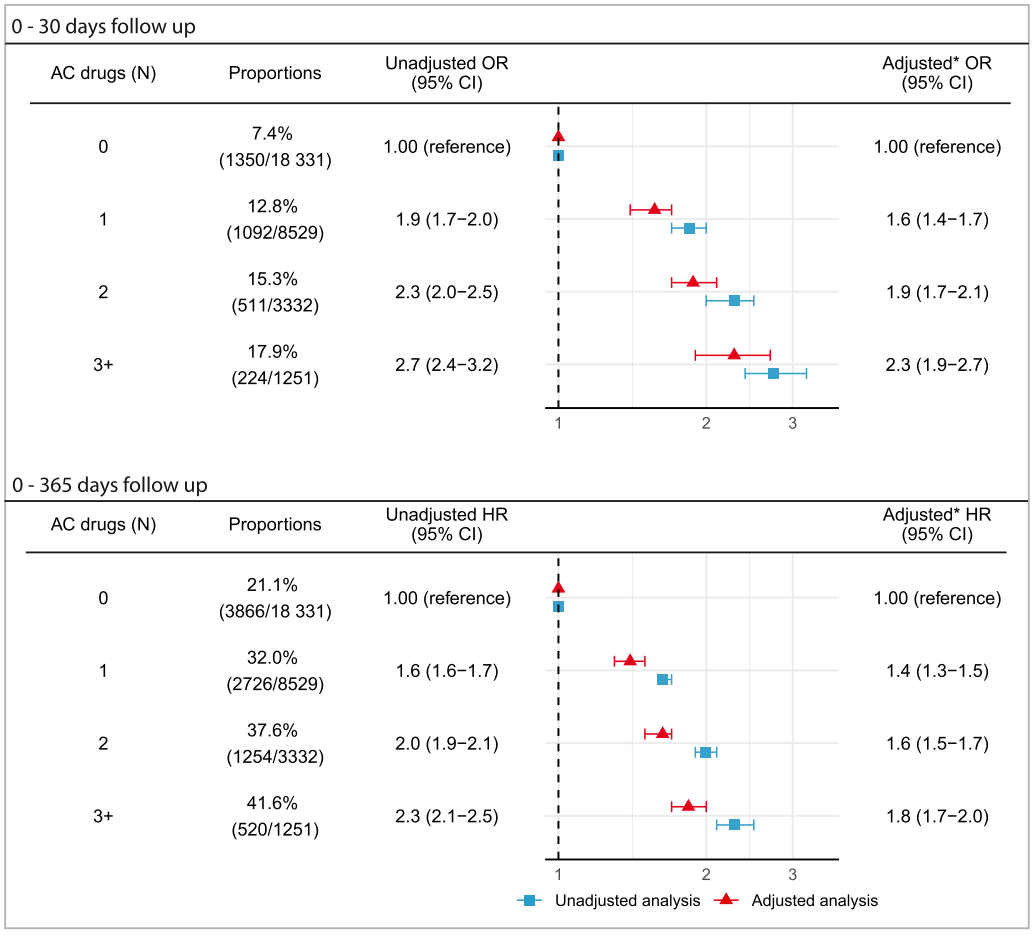

Fig. 4. Unadjusted and adjusted logistic regression analysis for number of anticholinergic (AC) drugs and 30-day mortality and unadjusted and adjusted cox regression analysis for number of AC drugs and 365-day mortality.
*Adjusted for age, sex and Charlson Comorbidity Index score
CI: Confidence interval
HR: Hazard Ratio
OR: Odds ratio.

which have addressed previous studies' risk of type II errors. Furthermore, the unselected study population with complete follow-up, enabled by the comprehensive nationwide registers, minimized risk of selection bias. All patients with hip fractures are treated at public hospitals, registrations in the DMHFR is mandatory, and validation of the hip fracture diagnoses has shown a positive predictive value above 90% (Hjelholt et al., 2020). Risk of information bias with regards to AC exposure should be acknowledged. Over-the-counter medications (i.e. antihistamines) are not registered in the National Patient Registry (Danish Health, 2019), potentially leading to non-differential misclassification. However, impact of over-the-counter medication on our study results is likely to be low since the administration of pharmacological treatment is controlled by municipal health-care workers in the majority of our patients. The exposure is defined on baseline use of AC drugs in a design resembling an intention to treat analysis. Discontinuation during follow up is a potential source of bias, however, the extent of discontinuation is most likely non-differential. If a difference between the groups is present, a previous study suggest that these differences would have to be very large in order to have a clinically important impact (Hempenius et al., 2021). Finally, the National Prescription Registry ensures information on all medication prescribed by physicians that is actually redeemed at pharmacies, however this does not cover actual drug consumption by the patients (Pottegård et al., 2017). A previous Danish publication suggest that non-adherence is not related to age but may be associated with polypharmacy (Pottegård et al., 2014). If this is the case in our study, this would most likely bias our results towards the null.

AC drugs are more often prescribed to patients with multiple comorbidities, some of which can independently increase mortality, and considering the distribution of CCI score among the AC exposure groups, confounding by indication is to some extend unavoidable. Drugs with AC properties does however cover a wide range of indications of heterogenous severity and no contradictory results after stratification by age, sex or CCI score were observed. Defining comorbidities by the CCI score also introduces a risk of residual confounding, as this score does not account for disease severity of the individual comorbidities. Despite these minor drawbacks, the CCI score have been validated as a dominant predictor of short- and long-term mortality following hip fractures (Charlson et al., 1987; Cher et al., 2019). Also, the diagnosis codes has been validated in the Danish National Patient Registry, showing a high positive predictive value (Thygesen et al., 2011).

4.3. Implications

Use of AC drugs was associated with mortality in older patients undergoing hip fracture surgery, but no clear relationship was demonstrated for an increasing ACB score and mortality in this study, nor in preceding studies including older surgical patients (Mangoni et al., 2013; Panula et al., 2009). Other scales summarizing AC burden include inconsistent numbers of drugs and are often in discordance regarding the potencies assigned to each medication (Lisibach et al., 2021). This obscures the clinical relevance of AC drugs' adverse effects and serve as an obstacle for practical applicability, further demonstrated by the varying associations according to the different AC scales applied (Mangoni et al., 2013). A more standardized risk assessment tool of AC exposure is still needed and counting the number of AC drugs may serve as a more comparable and apprehensible method for future research and clinical practice, substantiated by the clear relationship for higher numbers of AC drugs and mortality demonstrated in our study. A similar relationship between increasing count of AC drugs and mortality was demonstrated in a recent study of a Danish cohort of hospitalized older patients (Sørensen et al., 2021), suggesting AC drugs to be an important predictor of mortality and a crucial target of intervention in acutely admitted older patients. Finally, a somewhat concerning but also interesting baseline finding, was the prevalence of strong analgesics, psycholeptics and other drugs known to cause cognitive issues, dizziness and increased fall risk, both due to the anticholinergic side effects, but also through their main mechanism of action (American Geriatrics Society, 2015). Furthermore, many of these drugs are commonly prescribed on a questionable indication to control symptoms which may also be handled by non-pharmacological treatments (Fastbom & Johnell, 2015).

5. Conclusion

This study demonstrated that exposure to drugs with AC properties are related to excess mortality in older patients undergoing hip fracture surgery, emphasizing the necessity of continued optimization of patients' pharmacotherapy with reduction of AC exposure through deprescribing or substitution to alternative drugs when possible. Discrepancies were observed across AC quantification methodology and demonstration of a more clear association with AC burden and mortality using numbers of AC drugs may suggest this to be a clinically relevant AC risk assessment tool with increased comparability in research and implementability in clinical practice.

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Availability of data and material

The dataset used in this study cannot be made publicly available according to the Danish law on personal data. Approval from the National Health Service Register (http://www.sundhedsdatastyrelsen.dk/da/forskerservice [in Danish]) and the Danish Data Protection Agency (http://www.datatilsynet.dk/english/) and collaboration with a Danish research unit is compulsory to access data from the Danish Health Data Authority.

Ethics approval

According to Danish law, no approval was required from the scientific ethical committee, as this was an observational study without patient contact or clinical interventions. The study was reported to the Danish Data Protection Agency through registration at Aarhus University (record number: AU-2016-051-000001, sequential number 880).

Consent to participate

Due to the observational design no informed consent was needed from any participants according to Danish law.

Author contributions

Study conception and design: Anne Line Lund Birkmose, Pia Kjær Kristensen, Morten Madsen, Alma Bečić Pedersen and Thomas Johannesson Hjelholt. Material preparation and data collection was performed by Morten Madsen, Pia Kjær Kristensen, Alma Bečić Pedersen and Thomas Johannesson Hjelholt. Analysis and interpretation of the results: All authors. Preparing first draft of the manuscript: Anne Line Lund Birkmose. All authors commented on previous versions of the manuscript and critically revised the paper. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

All authors report no personal or economical conflicts of interest directly relevant to the content of this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2023.105017.

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